

## SUBSTITUTED QUINOBENZOXAZINE ANALOGS

### Cross-Reference to Related Applications

[0001] This application claims the benefit of U.S. provisional application 60/461,271, filed April 7, 2003; U.S. provisional application 60/463,171, filed April 15, 2003; U.S. provisional application 60/519,535, filed November 12, 2003; and U.S. provisional application 60/532,727, filed December 23, 2003. The contents of these documents are incorporated herein by reference.

### Field of the Invention

[0002] The invention relates to substituted quinobenzoxazines analogs, and methods of using such compounds.

### Background

[0003] Quadruplexes can form in certain purine-rich strands of nucleic acids. In duplex nucleic acids, certain purine rich strands are capable of engaging in a slow equilibrium between a typical duplex helix structure and in unwound and non-B-form regions. These unwound and non-B forms can be referred to as "paranemic structures." Some forms are associated with sensitivity to S1 nuclease digestion, which can be referred to as "nuclease hypersensitivity elements" or "NHEs." A quadruplex is one type of paranemic structure and certain NHEs can adopt a quadruplex structure. Considerable circumstantial evidence suggests that quadruplex structures can exist in vivo in specific regions of the genome, including the telomeric ends of chromosomes and oncogene regulatory regions. (Han, *et al.*, *Trends Pharm. Sci.* (2000) 21:136-142). Thus, quadruplex forming regions of DNA may be used as molecular targets for anticancer agents.

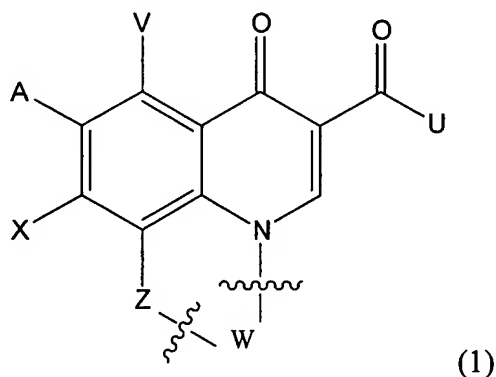
### Summary of the Invention

[0004] Compounds described herein interact with regions of DNA that can form quadruplexes and act as tumor suppression agents with reduced side effects. Such compounds reduce expression of highly proliferate genes and are utilized for treating cancers. Furthermore, the compounds may

also exhibit antibacterial or antiviral activity, and may be used for treating bacterial and viral infections.

[0005] Various embodiments of the present invention are described below. The present invention encompasses other compounds having formula 1, with substituents independently selected from compounds in Tables 1-3. Thus, the present invention is not limited to the specific combination of substituents described in various embodiments below.

[0006] The compounds have the general formula:



and pharmaceutically acceptable salts, esters and prodrugs thereof;

wherein V is H, halo, or  $\text{NR}^1\text{R}^2$ ;

A is H, fluoro, or  $\text{NR}^1_2$ ;

Z is O, S,  $\text{NR}^1$  or  $\text{CH}_2$ ;

U is  $\text{OR}^2$  or  $\text{NR}^1\text{R}^2$ ;

X is  $\text{OR}^2$ ,  $\text{NR}^1\text{R}^2$ , halo, azido, or  $\text{SR}^2$ ;

n is 1-3;

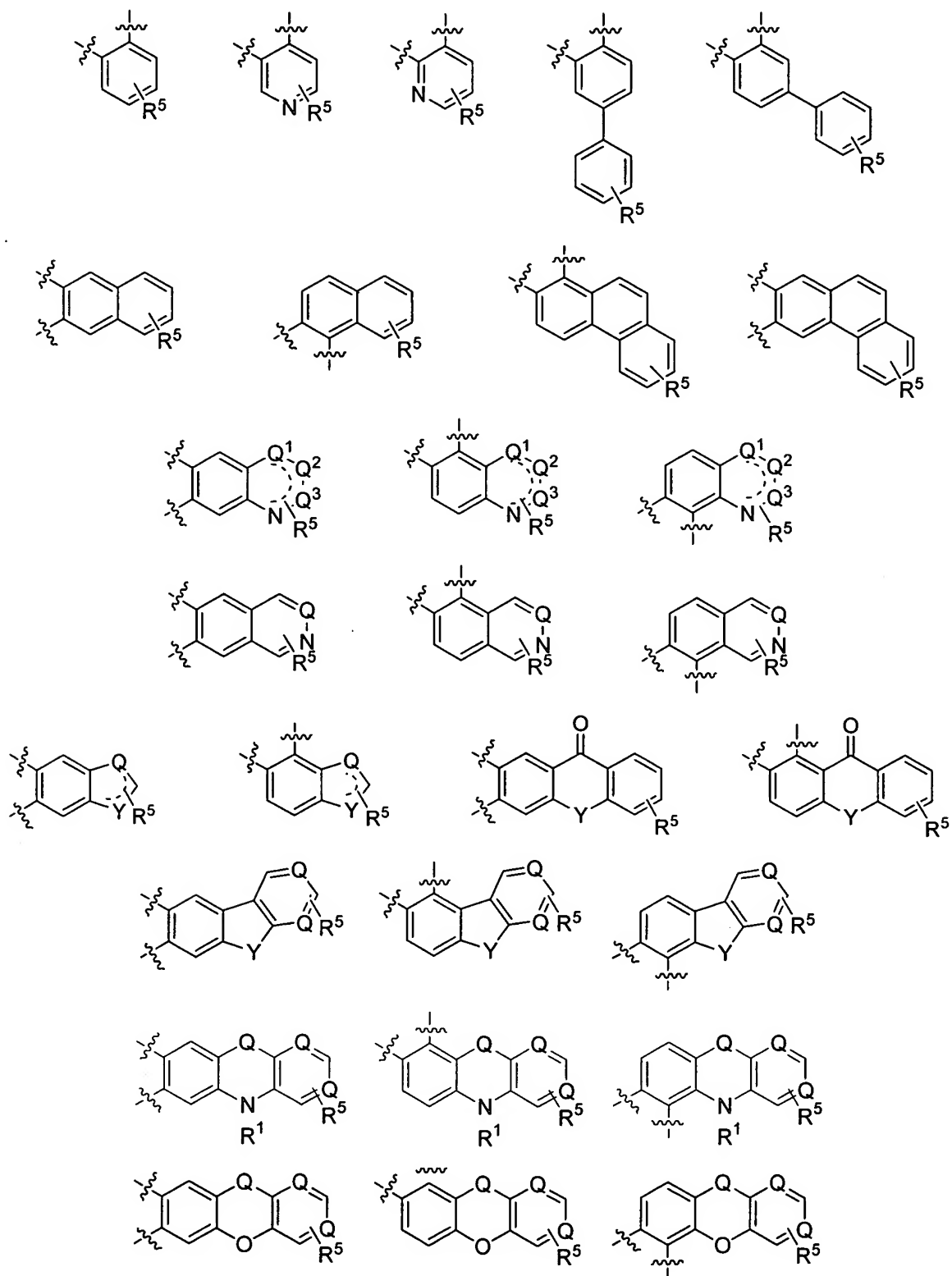
wherein in  $\text{NR}^1\text{R}^2$ ,  $\text{R}^1$  and  $\text{R}^2$  may form a double bond or a ring, each of which is optionally substituted;

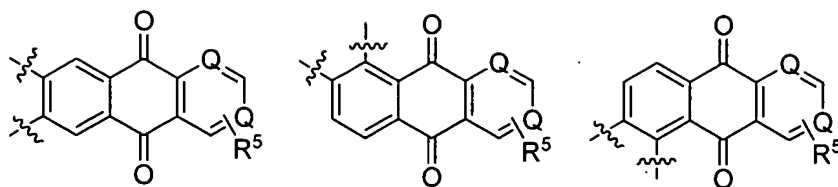
$\text{R}^1$  is H or a  $\text{C}_{1-6}$  alkyl;

$\text{R}^2$  is H or a  $\text{C}_{1-10}$  alkyl or  $\text{C}_{2-10}$  alkenyl optionally containing one or more non-adjacent heteroatoms selected from N, O, and S, and optionally substituted with a carbocyclic or heterocyclic ring; or  $\text{R}^2$  is an optionally substituted heterocyclic ring, aryl or heteroaryl;

W is selected from the group consisting of







wherein Q, Q<sup>1</sup>, Q<sup>2</sup>, and Q<sup>3</sup> are independently CH or N;

Y is independently O, CH, =O or NR<sup>1</sup>;

and R<sup>5</sup> is a substituent at any position on the fused ring; and is H, OR<sup>2</sup>, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, each optionally substituted by halo, =O or one or more heteroatoms; or R<sup>5</sup> is an inorganic substituent; or two adjacent R<sup>5</sup> is linked to obtain a 5-6 membered substituted or unsubstituted carbocyclic or heterocyclic ring, optionally fused to an additional substituted or unsubstituted carbocyclic or heterocyclic ring;

provided that U is not OR<sup>1</sup> when X is pyrrolidinyl; A is F; Z is O; and W is naphthalenyl or phenylene;

U is not morpholinyl or 2,4-difluoroaniline when X is F or pyrrolidinyl; A is F; Z is O; and W is phenylene; and

further provided that if U is OH, then W represents multiple fused aromatic rings and X is not halo; and X is NH<sub>2</sub>, or a moiety that does not contain N, or contains more than 6 carbons.

**[0007]** In the above formula 1, A and X may independently be halo. In one example, A and X may independently be fluoro.

**[0008]** In the above formula, V may be H. Alternatively, V may be NH<sub>2</sub> or a compound having the formula NR<sup>1</sup> – (CR<sup>1</sup><sub>2</sub>)<sub>n</sub> – NR<sup>3</sup>R<sup>4</sup>;

wherein R<sup>1</sup> and R<sup>3</sup> are independently H or C<sub>1-6</sub> alkyl;

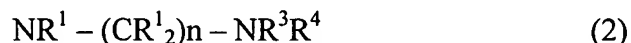
n is 1-6; and

R<sup>4</sup> is H, C<sub>1-6</sub> alkyl optionally substituted with a carbocyclic or heterocyclic ring, or aryl; and wherein in NR<sup>3</sup>R<sup>4</sup>, R<sup>3</sup> and R<sup>4</sup> may form an optionally substituted ring.

**[0009]** In the above formula 1, U and X may independently be NR<sup>1</sup>R<sup>2</sup>. In one example, R<sup>1</sup> is H and R<sup>2</sup> is a C<sub>1-10</sub> alkyl optionally containing one or more heteroatoms, and optionally substituted with a C<sub>3-6</sub> cycloalkyl, aryl or a 5-14 membered heterocyclic ring containing one or more N, O or S. In another example, R<sup>1</sup> is H and R<sup>2</sup> is an aryl or a 5-14 membered heterocyclic ring containing one or more N, O or S, each optionally substituted with an amino or another heterocyclic ring. In yet

another example, R<sup>1</sup> and R<sup>2</sup> in NR<sup>1</sup>R<sup>2</sup> form an optionally substituted 5-14 membered ring containing one or more N, O or S. In particular examples, NR<sup>1</sup>R<sup>2</sup> is morpholine, thiomorpholine, piperazine, piperidine or diazepine.

[0010] In the above formula 1, U and X may independently have the formula



wherein R<sup>1</sup> and R<sup>3</sup> are independently H or C<sub>1-6</sub> alkyl;

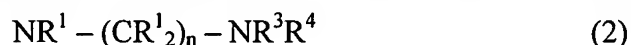
n is 1-6; and

R<sup>4</sup> is H or a C<sub>1-10</sub> alkyl or C<sub>2-10</sub> alkenyl optionally containing one or more non-adjacent heteroatoms selected from N, O and S, and optionally substituted with a carbocyclic or heterocyclic ring; and

wherein in NR<sup>3</sup>R<sup>4</sup>, R<sup>3</sup> and R<sup>4</sup> may form an optionally substituted ring.

[0011] In the above formula 2, n may be 2-3. In one example, NR<sup>3</sup>R<sup>4</sup> is an acyclic amine, or guanidinyll or a tautomer thereof; or R<sup>3</sup> and R<sup>4</sup> optionally form a substituted ring containing one or more N, O or S. In particular examples, NR<sup>3</sup>R<sup>4</sup> is morpholine, thiomorpholine, imidazole, pyrrolidine, piperazine, pyridine or piperidine.

[0012] In the above formula 1, X may be NR<sup>1</sup>R<sup>2</sup>; and U has the formula



wherein R<sup>1</sup> and R<sup>2</sup> are as defined in claim 1;

R<sup>3</sup> is H or C<sub>1-6</sub> alkyl;

n is 1-6; and

R<sup>4</sup> is H or a C<sub>1-10</sub> alkyl or C<sub>2-10</sub> alkenyl optionally containing one or more non-adjacent heteroatoms selected from N, O and S, and optionally substituted with a carbocyclic or heterocyclic ring; and

wherein in NR<sup>1</sup>R<sup>2</sup> and NR<sup>3</sup>R<sup>4</sup>, R<sup>1</sup> and R<sup>2</sup>, and R<sup>3</sup> and R<sup>4</sup> each independently may form a substituted ring.

[0013] In the above formula, where X is NR<sup>1</sup>R<sup>2</sup> and U has the formula NR<sup>1</sup> - (CR<sup>1</sup><sub>2</sub>)<sub>n</sub> - NR<sup>3</sup>R<sup>4</sup> (2), R<sup>1</sup> and R<sup>2</sup> in NR<sup>1</sup>R<sup>2</sup>, and R<sup>3</sup> and R<sup>4</sup> in NR<sup>3</sup>R<sup>4</sup> each may independently form a substituted ring containing one or more N, O or S. For example, X is optionally substituted with amino, carbamate, a C<sub>1-10</sub> alkyl containing one or more non-adjacent N, O or S, and optionally substituted with a heterocyclic ring; aryl or a saturated or unsaturated heterocyclic ring, each of which is optionally

substituted. In one example, X and  $\text{NR}^3\text{R}^4$  are independently morpholine, thiomorpholine, imidazole, pyrrolidine, piperazine, pyridine or piperidine. In one example, X and  $\text{NR}^3\text{R}^4$  are independently pyrrolidine. In another example, X is pyrrolidine substituted with pyrazine. In this example, V is H; A is fluoro; and W is naphthalenyl.

[0014] Examples of 5-6 membered heterocyclic rings include but are not limited to tetrahydrofuran, 1,3-dioxolane, 2,3-dihydrofuran, tetrahydropyran, benzofuran, isobenzofuran, 1,3-dihydro-isobenzofuran, isoxazole, 4,5-dihydroisoxazole, piperidine, pyrrolidine, pyrrolidin-2-one, pyrrole, pyridine, pyrimidine, octahydro-pyrrolo[3,4-*b*]pyridine, piperazine, pyrazine, morpholine, thiomorpholine, imidazole, imidazolidine-2,4-dione, benzimidazole, 1,3-dihydrobenzimidazol-2-one, indole, thiazole, benzothiazole, thiadiazole, thiophene, tetrahydro-thiophene 1,1-dioxide, diazepine, triazole, guanidine, diazabicyclo[2.2.1]heptane, 2,5-diazabicyclo[2.2.1]heptane, and 2,3,4,4a,9,9a-hexahydro-1H- $\beta$ -carboline.

[0015] In the above formula 1, W may be benzene, pyridine, biphenyl, naphthalene, phenanthrene, quinoline, isoquinoline, quinazoline, cinnoline, phthalazine, quinoxaline, indole, benzimidazole, benzoxazole, benzthiazole, benzofuran, anthrone, xanthone, acridone, fluorenone, carbazolyl, pyrimido[4,3-*b*]furan, pyrido[4,3-*b*]indole, pyrido[2,3-*b*]indole, dibenzofuran, acridine or acridizine.

[0016] In the above formula 1, U may be  $\text{OR}^2$  and  $\text{R}^2$  is a  $\text{C}_{1-6}$  alkyl optionally substituted with a carbocyclic or heterocyclic ring.

[0017] In the above formula 1, each optionally substituted moiety is substituted with one or more halo,  $\text{OR}^2$ ,  $\text{NR}^1\text{R}^2$ , carbamate,  $\text{C}_{1-10}$  alkyl,  $\text{C}_{2-10}$  alkenyl, each optionally substituted by halo, =O, aryl or one or more heteroatoms; inorganic substituents, aryl, carbocyclic or a heterocyclic ring.

[0018] The compounds of the present invention may be chiral. As used herein, a chiral compound is a compound that is different from its mirror image, and has an enantiomer. Methods of synthesizing chiral compounds and resolving a racemic mixture of enantiomers are well known to those skilled in the art. See, *e.g.*, March, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, (1985), which is incorporated herein by reference.

[0019] The present invention also provides pharmaceutical compositions comprising compounds having formula 1, and a pharmaceutically acceptable excipient.

[0020] Furthermore, the present invention provides methods for ameliorating a cell proliferative disorder, comprising administering to a subject in need thereof an effective amount of a compound having formula 1 or a pharmaceutical composition thereof, thereby ameliorating said cell-proliferative disorder. In one example, the cell proliferative disorder is cancer. In another example, cell proliferation is reduced, or cell death is induced. The subject may be human or animal.

[0021] The present invention also provides methods for reducing cell proliferation or inducing cell death, comprising contacting a system with an effective amount of a compound having formula 1 or a pharmaceutical composition thereof, thereby reducing cell proliferation or inducing cell death in said system. The system may be a cell or tissue.

[0022] The present invention further provides methods for reducing microbial titers, comprising contacting a system with an effective amount of a compound having formula 1 or a pharmaceutical composition thereof, thereby reducing microbial titers. The system may be a cell or tissue. In one example, the microbial titers are viral, bacterial or fungal titers.

[0023] Further, the present invention provides methods for ameliorating a microbial infection, comprising administering to a subject in need thereof an effective amount of a compound having formula 1 or a pharmaceutical composition thereof, thereby ameliorating said microbial infection. The subject may be human or animal. In one example, the microbial infection is viral, bacterial or fungal.

#### Description of the Figures

[0024] Figure 1 shows antitumor activity of a compound having formula 1 tested in a Ramos xenograft model.

[0025] Figure 2 shows antitumor activity of a compound having formula 1 tested in HCT 116.

#### Description of the Invention

[0026] The present invention relates to quinoline derivatives having formula 1, and pharmaceutically acceptable salts, esters, and prodrugs thereof. In particular embodiments, the compounds interact with regions of DNA that can form quadruplexes. The present invention also relates to methods for treating cancer, bacterial and viral infections using such compounds.

[0027] Because regions of DNA that can form quadruplexes are regulators of biological processes such as oncogene transcription, modulators of quadruplex biological activity can be utilized as cancer therapeutics. Molecules that interact with regions of DNA that can form quadruplexes can exert a therapeutic effect on certain cell proliferative disorders and related conditions. Particularly, abnormally increased oncogene expression can cause cell proliferative disorders and quadruplex structures typically down-regulate oncogene expression. Examples of oncogenes include but are not limited to MYC, HIF, VEGF, ABL, TGF, PDGFA, MYB, SPARC, HUMTEL, HER, VAV, RET, H-RAS, EGF, SRC, BCL1, BCL2, and other oncogenes known to one of skill in the art.

[0028] Molecules that bind to regions of DNA that can form quadruplexes can exert a biological effect according to different mechanisms, which include for example, stabilizing a native quadruplex structure, inhibiting conversion of a native quadruplex to duplex DNA by blocking strand cleavage, and stabilizing a native quadruplex structure having a quadruplex-destabilizing nucleotide substitution and other sequence specific interactions. Thus, compounds that bind to regions of DNA that can form quadruplexes described herein may be administered to cells, tissues, or organisms for the purpose of down-regulating oncogene transcription and thereby treating cell proliferative disorders. The terms “treatment” and “therapeutic effect” as used herein refer to reducing or stopping a cell proliferation rate (*e.g.*, slowing or halting tumor growth) or reducing the number of proliferating cancer cells (*e.g.*, removing part or all of a tumor).

[0029] Determining whether the biological activity of native DNA that can form quadruplexes is modulated in a cell, tissue, or organism can be accomplished by monitoring quadruplex biological activity. Quadruplex forming regions of DNA biological activity may be monitored in cells, tissues, or organisms, for example, by detecting a decrease or increase of gene transcription in response to contacting the quadruplex forming DNA with a molecule. Transcription can be detected by directly observing RNA transcripts or observing polypeptides translated by transcripts, which are methods well known in the art.

[0030] Molecules that interact with quadruplex forming DNA and quadruplex forming nucleic acids can be utilized to treat many cell proliferative disorders. Cell proliferative disorders include, for example, colorectal cancers and hematopoietic neoplastic disorders (*i.e.*, diseases involving hyperplastic/neoplastic cells of hematopoietic origin such as those arising from myeloid, lymphoid

or erythroid lineages, or precursor cells thereof). The diseases can arise from poorly differentiated acute leukemias, *e.g.*, erythroblastic leukemia and acute megakaryoblastic leukemia. Additional myeloid disorders include, but are not limited to, acute promyeloid leukemia (APML), acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) (Vaickus, Crit. Rev. in *Oncol./Hematol.* 11:267-297 (1991)). Lymphoid malignancies include, but are not limited to acute lymphoblastic leukemia (ALL), which includes B-lineage ALL and T-lineage ALL, chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HLL) and Waldenstrom's macroglobulinemia (WM). Additional forms of malignant lymphomas include, but are not limited to non-Hodgkin lymphoma and variants thereof, peripheral T cell lymphomas, adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGL), Hodgkin's disease and Reed-Sternberg disease. Cell proliferative disorders also include cancers of the colorectum, breast, lung, liver, pancreas, lymph node, colon, prostate, brain, head and neck, skin, liver, kidney, and heart. Compounds that interact with regions of DNA that can form quadruplexes also can be utilized to target cancer related processes and conditions, such as increased angiogenesis, by inhibiting angiogenesis in a subject.

[0031] The present invention provides a method for reducing cell proliferation or for treating or alleviating cell proliferative disorders, comprising contacting a system having a DNA capable of forming a quadruplex with a compound having formula 1. The system may be a group of cells or one or more tissues. In one embodiment, the system is a subject in need of a treatment of a cell proliferative disorder (*e.g.*, a mammal such as a mouse, rat, monkey, or human). The present invention also provides a method for treating colorectal cancer by administering a compound that interacts with a c-MYC quadruplex forming region to a subject in need thereof, thereby reducing the colorectal cancer cell proliferation. Furthermore, the present invention provides a method for inhibiting angiogenesis and optionally treating a cancer associated with angiogenesis, comprising administering a compound that interacts with a vascular endothelial growth factor (VEGF) quadruplex forming region to a subject in need thereof, thereby reducing angiogenesis and optionally treating a cancer associated with angiogenesis.

[0032] As used herein, the term "alkyl" refers to a carbon-containing compound, and encompasses compounds containing one or more heteroatoms. The term "alkyl" also encompasses compounds substituted with one or more non-interfering substituents. Examples of non-interfering

substituents include but are not limited to OR<sup>1</sup>, amino, amido, halo, =O, aryl, heterocyclic groups, or inorganic substituents, and other substituents that do not interfere with the activity of the compound.

[0033] As used herein, the term “carbocycle” refers to a cyclic compound containing only carbon atoms in the ring.

[0034] As used herein, the term “heterocycle” refers to a cyclic compound comprising a heteroatom, including monocyclic or bicyclic heterocycles. As used herein, the term “heteroatom” refers to any atom that is not carbon or hydrogen, such as nitrogen, oxygen or sulfur. Examples of heterocycles include but are not limited to oxirane, oxetane, pyran, tetrahydropyran, dioxane, lactones, aziridine, azetidine, pyrrolidine, piperidine, morpholine, lactams, and tetrahydrofuran.

[0035] As used herein, the term “bicyclic compound” refers to a compound having two rings which share a pair of bridgehead carbon atoms. Examples of bicyclic compounds include but are not limited to decalin, norbornane, camphor, and diazabicyclo[2.2.1]heptane.

[0036] As used herein, the terms “heteroaryl” or “heteroaromatic” refer to an aromatic heterocycle. Examples of heteroaryls include but are not limited to furan, pyrrole, pyridine, pyrimidine, imidazole, or triazole.

[0037] The terms “treat,” “treatment” and “therapeutic effect” as used herein refer to reducing or stopping a cell proliferation rate (*e.g.*, slowing or halting tumor growth) or reducing the number of proliferating cancer cells (*e.g.*, removing part or all of a tumor). These terms also are applicable to reducing a titre of a microorganism in a system (*i.e.*, cell, tissue, or subject) infected with a microorganism, reducing the rate of microbial propagation, reducing the number of symptoms or an effect of a symptom associated with the microbial infection, and/or removing detectable amounts of the microbe from the system. Examples of microorganism include but are not limited to virus, bacterium and fungus.

[0038] Compounds that interact with quadruplex forming regions of DNA can also be used to reduce a microbial infection, such as a viral infection. Retroviruses offer a wealth of potential targets for G-quadruplex targeted therapeutics. G-quadruplex structures have been implicated as functional elements in at least two secondary structures formed by either viral RNA or DNA in HIV, the dimer linker structure (DLS) and the central DNA flap (CDF). Additionally, DNA aptamers which are able to adopt either inter- or intramolecular quadruplex structures are able to



inhibit viral replication. In one example, DNA aptamers are able to inhibit viral replication by targeting the envelope glycoprotein (putatively). In another example, DNA aptamers inhibit viral replication by targeting the HIV-integrase respectively, suggesting the involvement of native quadruplex structures in interaction with the integrase enzyme.

[0039] Dimer linker structures, which are common to all retroviruses, serve to bind two copies of the viral genome together by a non-covalent interaction between the two 5' ends of the two viral RNA sequences. The genomic dimer is stably associated with the gag protein in the mature virus particle. In the case of HIV, the origin of this non-covalent binding may be traced to a 98 base-pair sequence containing several runs of at least two consecutive guanines (*e.g.*, the 3' for the formation of RNA dimers *in vitro*). An observed cation (potassium) dependence for the formation and stability of the dimer *in vitro*, in addition to the failure of an antisense sequence to effectively dimerize, has revealed the most likely binding structure to be an intermolecular G-quadruplex.

[0040] Prior to integration into the host genome, reverse transcribed viral DNA forms a pre-integration complex (PIC) with at least two major viral proteins, integrase and reverse transcriptase, which is subsequently transported into the nucleus. The Central DNA Flap (CDF) refers to 99-base length single-stranded tail of the + strand, occurring near the center of the viral duplex DNA, which is known to play a role in the nuclear import of the PIC. Oligonucleotide mimics of the CDF have been shown to form intermolecular G-quadruplex structures in cell-free systems.

[0041] Thus, compounds that recognize quadruplex forming regions can be used to stabilize the dimer linker structure and thus prevent de-coupling of the two RNA strands. Also, by binding to the quadruplex structure formed by the CDF, protein recognition and/or binding events for nuclear transport of the PIC may be disrupted. In either case, a substantial advantage can exist over other anti-viral therapeutics. Current Highly Active Anti-Retroviral Therapeutic (HAART) regimes rely on the use of combinations of drugs targeted towards the HIV protease and HIV integrase. The requirement for multi-drug regimes is to minimize the emergence of resistance, which will usually develop rapidly when agents are used in isolation. The source of such rapid resistance is the infidelity of the reverse transcriptase enzyme which makes a mutation approximately once in every 10,000 base pairs. An advantage of targeting viral quadruplex structures over protein targets, is that the development of resistance is slow or is impossible. A point mutation of the target quadruplex

can compromise the integrity of the quadruplex structure and lead to a non-functional copy of the virus. A single therapeutic agent based on this concept may replace the multiple drug regimes currently employed, with the concomitant benefits of reduced costs and the elimination of harmful drug/drug interactions.

[0042] The present invention provides a method for reducing a microbial titer in a system, comprising contacting a system having a native DNA quadruplex forming region with a compound having formula 1. The system may be one or more cells or tissues. Examples of microbial titers include but are not limited to viral, bacterial or fungal titers. In a particular embodiment, the system is a subject in need of a treatment for a viral infection (*e.g.*, a mammal such as a mouse, rat, monkey, or human). Examples of viral infections include infections by a hepatitis virus (*e.g.*, hepatitis B or C), human immunodeficiency virus (HIV), rhinovirus, herpes-zoster virus (VZV), herpes simplex virus (*e.g.*, HSV-1 or HSV-2), cytomegalovirus (CMV), vaccinia virus, influenza virus, encephalitis virus, hantavirus, arbovirus, West Nile virus, human papilloma virus (HPV), Epstein-Barr virus, and respiratory syncytial virus. The present invention also provides a method for treating HIV infection by administering a compound having formula 1 to a subject in need thereof, thereby reducing the HIV infection.

Identifying compounds that can bind to quadruplex forming regions of DNA

[0043] Compounds described herein are identified as compounds that can bind to quadruplex forming regions of DNA where a biological activity of this region, often expressed as a “signal,” produced in a system containing the compound is different than the signal produced in a system not containing the compound. While background signals may be assessed each time a new molecule is probed by the assay, detecting the background signal is not required each time a new molecule is assayed.

[0044] Examples of quadruplex forming nucleic acid sequences are set forth in the following Table A:

**Table A**

<u>SEQUENCE</u>	<u>SEQ ID NO</u>	<u>ORIGIN</u>
TG <sub>4</sub> AG <sub>3</sub> TG <sub>4</sub> AG <sub>3</sub> TG <sub>4</sub> AAGG	1	<i>CMYC</i>
GGGGGGGGGGGGGGCGGGGGCGGGGGCGGGGGAGGGGC	2	<i>PDGFA</i>
G <sub>8</sub> ACGCG <sub>3</sub> AGCTG <sub>5</sub> AG <sub>3</sub> CTTG <sub>4</sub> CCAG <sub>3</sub> CG <sub>4</sub> CGCTTAG <sub>5</sub>	3	<i>PDGFB/c -sis</i>
AGGAAGGGGAGGGCCGGGGGGAGGTGGC	4	<i>CABL</i>
AGGGGCGGGGCGGGGCGGGGGC	5	<i>RET</i>
GGGAGGAAGGGGGCGGGAGCGGGGC	6	<i>BCL-2</i>
GGGGGGCGGGGGCGGGGCGCAGGGGGAGGGGGC	7	<i>Cyclin D1/BCL-1</i>
CGGGGCGGGGCGGGGGCGGGGGC	8	<i>H-RAS</i>
AGAGGAGGAGGAGGTCACGGAGGAGGAGGAGAAGGAGGAGGAGGAA	9	<i>CMYB</i>
(GGA) <sub>4</sub>	10	<i>VAV</i>
AGAGAAGAGGGGAGGAGGAGGAGGAGGAGGAGGAGGCGC	11	<i>HMGA2</i>
GGAGGGGGAGGGG	12	<i>CPIM</i>
AGGAGAAGGAGGAGGTGGAGGAGGAGG	13	<i>HER2/neu</i>
AGGAGGAGGAGAATGCGAGGAGGAGGGAGGAGA	14	<i>EGFR</i>
GGGGCGGGCCGGGGGCGGGGTCCCGGCGGGGCGGAG	15	<i>VEGF</i>
CGGGAGGAGGAGGAAGGAGGAAGCGCG	16	<i>CSRC</i>

[0045] In addition to determining whether a test molecule or test nucleic acid gives rise to a different signal, the affinity of the interaction between the nucleic acid and the compound may be quantified. IC<sub>50</sub>, K<sub>d</sub>, or K<sub>i</sub> threshold values may be compared to the measured IC<sub>50</sub> or K<sub>d</sub> values for each interaction, and thereby identify a test molecule as a quadruplex interacting molecule or a test nucleic acid as a quadruplex forming nucleic acid. For example, IC<sub>50</sub> or K<sub>d</sub> threshold values of 10 μM or less, 1 μM or less, and 100 nM or less are often utilized. In another example, threshold values of 10 nM or less, 1 nM or less, 100 pM or less, and 10 pM or less may be utilized to identify quadruplex interacting molecules and quadruplex forming nucleic acids.

[0046] Many assays are available for identifying compounds that have affinity for quadruplex forming regions of DNA. In some of these assays, the biological activity is the quadruplex nucleic

acid binding to a compound and binding is measured as a signal. In other assays, the biological activity is a polymerase arresting function of a quadruplex and the degree of arrest is measured as a decrease in a signal. In certain assays, the biological activity is transcription and transcription levels can be quantified as a signal. In another assay, the biological activity is cell death and the number of cells undergoing cell death is quantified. Another assay monitors proliferation rates of cancer cells. Examples of assays are fluorescence binding assays, gel mobility shift assays (see, *e.g.*, Jin & Pike, *Mol. Endocrinol.* (1996) 10:196-205), polymerase arrest assays, transcription reporter assays, cancer cell proliferation assays, and apoptosis assays (see, *e.g.*, Amersham Biosciences (Piscataway, New Jersey)), and embodiments of such assays are described hereafter. Also, topoisomerase assays can be utilized to determine whether the quadruplex interacting molecules have a topoisomerase pathway activity (see, *e.g.*, TopoGEN, Inc. (Columbus, Ohio)).

#### Gel Electrophoretic Mobility Shift Assay (EMSA)

[0047] An EMSA is useful for determining whether a nucleic acid forms a quadruplex and whether a nucleotide sequence is quadruplex-destabilizing. EMSA is conducted as described previously (Jin & Pike, *Mol. Endocrinol.* 10: 196-205 (1996)) with minor modifications. Generally, synthetic single-stranded oligonucleotides are labeled in the 5' -terminus with T4-kinase in the presence of [ $\gamma$ - $^{32}$ P] ATP (1,000 mCi/mmol, Amersham Life Science) and purified through a sephadex column.  $^{32}$ P-labeled oligonucleotides (~30,000 cpm) are then incubated with or without various concentrations of a testing compound in 20  $\mu$ l of a buffer containing 10 mM Tris pH 7.5, 100 mM KCl, 5 mM dithiothreitol, 0.1 mM EDTA, 5 mM MgCl<sub>2</sub>, 10% glycerol, 0.05% Nonedit P-40, and 0.1 mg/ml of poly(dI-dC) (Pharmacia). After incubation for 20 minutes at room temperature, binding reactions are loaded on a 5% polyacrylamide gel in 0.25 x Tris borate-EDTA buffer (0.25 x TBE, 1 x TBE is 89 mM Tris-borate, pH 8.0, 1 mM EDTA). The gel is dried and each band is quantified using a phosphoimager.

#### DMS Methylation Protection Assay

[0048] Chemical footprinting assays are useful for assessing quadruplex structure. Quadruplex structure is assessed by determining which nucleotides in a nucleic acid are protected or unprotected from chemical modification as a result of being inaccessible or accessible, respectively, to the

modifying reagent. A DMS methylation assay is an example of a chemical footprinting assay. In such an assay, bands from EMSA are isolated and subjected to DMS-induced strand cleavage. Each band of interest is excised from an electrophoretic mobility shift gel and soaked in 100 mM KCl solution (300  $\mu$ l) for 6 hours at 4°C. The solutions are filtered (microcentrifuge) and 30,000 cpm (per reaction) of DNA solution is diluted further with 100 mM KCl in 0.1X TE to a total volume of 70  $\mu$ l (per reaction). Following the addition of 1  $\mu$ l salmon sperm DNA (0.1  $\mu$ g/ $\mu$ l), the reaction mixture is incubated with 1  $\mu$ l DMS solution (DMS:ethanol; 4:1; v:v) for a period of time. Each reaction is quenched with 18  $\mu$ l of stop buffer (b-mercaptoethanol:water:NaOAc (3 M); 1:6:7; v:v:v). Following ethanol precipitation (twice) and piperidine cleavage, the reactions are separated on a preparative gel (16%) and visualized on a phosphorimager.

#### Polymerase Arrest Assay

**[0049]** An arrest assay includes a template nucleic acid, which may comprise a quadruplex forming sequence, and a primer nucleic acid which hybridizes to the template nucleic acid 5' of the quadruplex-forming sequence. The primer is extended by a polymerase (*e.g.*, Taq polymerase), which advances from the primer along the template nucleic acid. In this assay, a quadruplex structure can block or arrest the advance of the enzyme, leading to shorter transcription fragments. Also, the arrest assay may be conducted at a variety of temperatures, including 45°C and 60°C, and at a variety of ion concentrations.

**[0050]** An example of the Taq polymerase stop assay is described in Han, *et al.*, *Nucl. Acids Res.* (1999) 27:537-542, which is a modification of that used by Weitzmann, *et al.*, *J. Biol. Chem.* (1996) 271:20958-20964. Briefly, a reaction mixture of template DNA (50 nM), Tris·HCl (50 mM), MgCl<sub>2</sub> (10 mM), DTT (0.5 mM), EDTA (0.1 mM), BSA (60 ng), and 5'-end-labeled quadruplex nucleic acid (~18 nM) is heated to 90°C for 5 minutes and allowed to cool to ambient temperature over 30 minutes. Taq Polymerase (1  $\mu$ l) is added to the reaction mixture, and the reaction is maintained at a constant temperature for 30 minutes. Following the addition of 10  $\mu$ l stop buffer (formamide (20 ml), 1 M NaOH (200  $\mu$ l), 0.5 M EDTA (400  $\mu$ l), and 10 mg bromophenol blue), the reactions are separated on a preparative gel (12%) and visualized on a phosphorimager. Adenine sequencing (indicated by "A" at the top of the gel) is performed using double-stranded DNA Cycle Sequencing System from Life Technologies. The general sequence for

the template strands is TCCAACATGTATAC-INSERT-TTAGCGACACGCAATTGCTATAGTGAGTCGTATTA, where "INSERT" refers to a nucleic acid sequence comprising a quadruplex forming sequence (See *e.g.*, Table A). Bands on the gel that exhibit slower mobility are indicative of quadruplex formation.

#### High Throughput Polymerase Arrest Assay

[0051] A high throughput polymerase arrest assay has been developed. The assay comprises contacting a template nucleic acid, often DNA, with a primer, which also is often DNA; contacting the primer/template complex with a compound described herein (also referred to as a "test compound"); contacting the primer/template complex with a polymerase; and separating reaction products. The assay often includes the step of denaturing the primer/template complex mixture and then renaturing the complex, which often is carried out before a test molecule is added to the system. Multiple assays often are carried out using varying concentrations of a test compound, such that an IC<sub>50</sub> value can be obtained, for example. The reaction products often include extended primers of different lengths. Where a test compound does not significantly interact with a quadruplex structure in the template, the primer often is extended to the end of the template.

[0052] Where a test compound significantly interacts with a quadruplex structure in the template, the primer often is extended only to the quadruplex structure in the template and no further. Thus, the reaction mixture often includes at least two reaction products when a test compound interacts with a quadruplex structure in the template, one having a completely extended primer and one having an incompletely extended primer, and these two reaction products are separated. The products may be separated using any convenient separation method, such as mass spectrometry and in one embodiment, capillary electrophoresis.

[0053] The reaction products often are identified by detecting a detectable label linked to the primer. The detectable label may be non-covalently linked to the 5' end of the primer (*e.g.*, a biotin molecule covalently linked to the 5' end of the primer which is non-covalently linked to an avidin molecule joined to a detectable label). The detectable label may be joined to the primer at any stage of the assay, sometimes before the primer is added to the system, after the primer is extended, or after the products are separated. The detectable label often is covalently linked to the primer using a procedure selected based upon the nature of the chemical groups in the detectable label.

**[0054]** Many methods for covalently linking detectable labels to nucleic acids are available, such as chemically coupling an allylamine-derivatized nucleotide to a succinimidyl-ester derivative of a detectable label, and then generating a primer using the labeled nucleotide. (See, *e.g.*, *Nature Biotech* (2000) 18:345-348 and [http address info.med.yale.edu/genetics/ward/tavi/n\\_coupling.html](http://info.med.yale.edu/genetics/ward/tavi/n_coupling.html)). A spacer (often between 5-16 carbon atoms long) sometimes is incorporated between the detectable label and the nucleotide. Any convenient detectable label may be utilized, including but not limited to a radioactive isotope (*e.g.*,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$ ,  $^{32}\text{P}$ ,  $^{14}\text{C}$  or  $^3\text{H}$ ); a light scattering label (*e.g.*, a spherical gold or silver label; Genicon Sciences Corporation, San Diego, CA and U.S. Patent No. 6,214,560); an enzymic or protein label (*e.g.*, GFP or peroxidase); or another chromogenic label or dye sometimes is utilized. Often, a fluorescent label is utilized (*e.g.*, amino-methyl coumarin (AMCA); diethyl aminomethyl coumarin (DEAC); cascade blue (CB); fluorescein isothiocyanate (FITC); Oregon green (OG); Alexa 488 (A488); rhodamine green (RGr); lanthanide chelate (*e.g.*, europium), carboxy-rhodamine 6G (R6G); tetramethyl rhodamine (TAMRA); Texas Red (TxR); Cy3; Cy3.5; Cy5, Cy5.5 and carboxynaphtofluorescein (CNF), digoxigenin (DIG); and 2,4-dinitrophenyl (DNP)). Other fluorophores and attendant excitation and emission wavelengths are described in Anantha, *et al.*, *Biochemistry* (1998) 37:2709-2714 and Qu & Chaires, *Methods Enzymol* (2000) 321:353-369).

**[0055]** In an embodiment, a primer oligonucleotide covalently linked to a fluorescent label is contacted with template DNA. The resulting complex is contacted with a test molecule and then contacted with a polymerase capable of extending the primer. The reaction products then are separated and detected by capillary electrophoresis. A longer primer sequence was used for practicing this embodiment as compared to embodiments where the primer includes no covalently-linked fluorophore or where capillary electrophoresis is not utilized for separation. Deoxynucleotides are added at any stage of the assay before the separation, often when the primer is contacted with the template DNA. The template DNA/primer complex often is denatured (*e.g.*, by increasing the temperature of the system) and then renatured (*e.g.*, by cooling the system) before a test compound is added).

**[0056]** The following is a specific example of the assay embodiment. A 5'-fluorescent-labeled (FAM) primer (P45, 15 nM) was mixed with template DNA (15 nM) in a Tris-HCL buffer (15 mM Tris, pH 7.5) containing 10 mM  $\text{MgCl}_2$ , 0.1 mM EDTA and 0.1 mM mixed deoxynucleotide

triphosphates (dNTP's). The FAM-P45 primer (5'-6FAM-AGTCTGAC TGACTGTACGTAGCTAATACGACTCACTATAGCAATT-3') and the template DNA (5'-TCCAACCTATGTATACTGGGGAGGGTGGGGAGGGTGGGGAAGGTTAGCGACACGCA ATTGCTATAGTGAGTCGTATTAGCTACGTACAGTCAGTCAGACT-3') were synthesized and HPLC purified by Applied Biosystems. The mixture was denatured at 95°C for 5 minutes and, after cooling down to room temperature, was incubated at 37°C for 15 minutes.

[0057] After cooling down to room temperature, 1 mM KCl<sub>2</sub> and the test compound (various concentrations) were added and the mixture incubated for 15 minutes at room temperature. The primer extension was performed by adding 10 mM KCl and Taq DNA Polymerase (2.5 U/reaction, Promega) and incubating at 70°C for 30 minutes. The reaction was stopped by adding 1 µl of the reaction mixture to 10 µl Hi-Di Formamide mixed and 0.25 µl LIZ120 size standard. Hi-Di Formamide and LIZ120 size standard were purchased from Applied Biosystems. The partially extended quadruplex arrest product was between 61 or 62 bases long and the full-length extended product was 99 bases long. The products were separated and analyzed using capillary electrophoresis. Capillary electrophoresis was performed using an ABI PRISM 3100-Avant Genetic Analyzer. The assay was performed using compounds described above and results are shown in Table 1. µM concentrations reported in Table 1 are concentrations at which 50% of the DNA was arrested in the assay (*i.e.*, the ratio of shorter partially extended DNA (arrested DNA) to full-length extended DNA is 1:1).

#### Transcription Reporter Assay

[0058] In a transcription reporter assay, test quadruplex DNA is coupled to a reporter system, such that a formation or stabilization of a quadruplex structure can modulate a reporter signal. An example of such a system is a reporter expression system in which a polypeptide, such as luciferase or green fluorescent protein (GFP), is expressed by a gene operably linked to the potential quadruplex forming nucleic acid and expression of the polypeptide can be detected. As used herein, the term "operably linked" refers to a nucleotide sequence which is regulated by a sequence comprising the potential quadruplex forming nucleic acid. A sequence may be operably linked when it is on the same nucleic acid as the quadruplex DNA, or on a different nucleic acid. An exemplary luciferase reporter system is described herein.



[0059] A luciferase promoter assay described in He, *et al.*, *Science* (1998) 281:1509-1512 often is utilized for the study of quadruplex formation. Specifically, a vector utilized for the assay is set forth in reference 11 of the He, *et al.*, document. In this assay, HeLa cells are transfected using the lipofectamin 2000-based system (Invitrogen) according to the manufacturer's protocol, using 0.1 µg of pRL-TK (Renilla luciferase reporter plasmid) and 0.9 µg of the quadruplex-forming plasmid. Firefly and Renilla luciferase activities are assayed using the Dual Luciferase Reporter Assay System (Promega) in a 96-well plate format according to the manufacturer's protocol.

#### Circular Dichroism Assay

[0060] Circular dichroism (CD) is utilized to determine whether another molecule interacts with a quadruplex nucleic acid. CD is particularly useful for determining whether a PNA or PNA-peptide conjugate hybridizes with a quadruplex nucleic acid *in vitro*. PNA probes are added to quadruplex DNA (5 µM each) in a buffer containing 10 mM potassium phosphate (pH 7.2) and 10 or 250 mM KCl at 37°C and then allowed to stand for 5 minutes at the same temperature before recording spectra. CD spectra are recorded on a Jasco J- 715 spectropolarimeter equipped with a thermoelectrically controlled single cell holder. CD intensity normally is detected between 220 nm and 320 nm and comparative spectra for quadruplex DNA alone, PNA alone, and quadruplex DNA with PNA are generated to determine the presence or absence of an interaction (see, *e.g.*, Datta, *et al.*, *JACS* (2001) 123:9612-9619). Spectra are arranged to represent the average of eight scans recorded at 100 nm/min.

#### Fluorescence Binding Assay

[0061] An example of a fluorescence binding assay is a system that includes a quadruplex nucleic acid, a signal molecule, and a test molecule. The signal molecule generates a fluorescent signal when bound to the quadruplex nucleic acid (*e.g.*, N-methylmesoporphyrin IX (NMM)), and the signal is altered when a test compound competes with the signal molecule for binding to the quadruplex nucleic acid. An alteration in the signal when test molecule is present as compared to when test compound is not present identifies the test compound as a quadruplex interacting compound.

[0062] 50  $\mu$ l of quadruplex nucleic acid or a nucleic acid not capable of forming a quadruplex is added in 96-well plate. A test compound also is added in varying concentrations. A typical assay is carried out in 100  $\mu$ l of 20 mM HEPES buffer, pH 7.0, 140 mM NaCl, and 100 mM KCl. 50  $\mu$ l of the signal molecule NMM then is added for a final concentration of 3  $\mu$ M. NMM is obtained from Frontier Scientific Inc, Logan, Utah. Fluorescence is measured at an excitation wavelength of 420 nm and an emission wavelength of 660 nm using a FluroStar 2000 fluorometer (BMG Labtechnologies, Durham, NC). Fluorescence often is plotted as a function of concentration of the test compound or quadruplex-targeted nucleic acid and maximum fluorescent signals for NMM are assessed in the absence of these molecules.

#### Cell Proliferation Assay

[0063] In a cancer cell proliferation assay, cell proliferation rates are assessed as a function of different concentrations of test compounds added to the cell culture medium. Any cancer cell type can be utilized in the assay. In one embodiment, colon cancer cells are cultured *in vitro* and test compounds are added to the culture medium at varying concentrations. A useful colon cancer cell line is colo320, which is a colon adenocarcinoma cell line deposited with the National Institutes of Health as accession number JCRB0225. Parameters for using such cells are available at the http address [cellbank.nihs.go.jp/cell/data/jcrb0225.htm](http://cellbank.nihs.go.jp/cell/data/jcrb0225.htm).

#### Formulation of Compounds

[0064] As used herein, the term "pharmaceutically acceptable salts, esters and amides" includes but are not limited to carboxylate salts, amino acid addition salts, esters and amides of the compounds, as well as the zwitterionic forms thereof, which are known to those skilled in the art as suitable for use with humans and animals. (See, *e.g.*, Gerge, S.M., *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.* (1977) 66:1-19, which is incorporated herein by reference.)

[0065] Any suitable formulation of the compounds described herein can be prepared. In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids that form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate,

succinate, benzoate, ascorbate,  $\alpha$ -ketoglutarate, and  $\alpha$ -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts. Pharmaceutically acceptable salts are obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (*e.g.*, sodium, potassium or lithium) or alkaline earth metal (*e.g.*, calcium) salts of carboxylic acids also are made.

[0066] A compound may be formulated as a pharmaceutical composition and administered to a mammalian host in need of such treatment. In one embodiment, the mammalian host is human. Any suitable route of administration may be used, including but not limited to oral, parenteral, intravenous, intramuscular, topical and subcutaneous routes.

[0067] In one embodiment, a compound is administered systemically (*e.g.*, orally) in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, compressed into tablets, or incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

[0068] Tablets, troches, pills, capsules, and the like also may contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and

propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Any material used in preparing any unit dosage form is pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

[0069] The active compound also may be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts may be prepared in a buffered solution, often phosphate buffered saline, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. The compound is sometimes prepared as a polymatrix-containing formulation for such administration (*e.g.*, a liposome or microsome). Liposomes are described for example in U.S. Patent No. 5,703,055 (Felgner, *et al.*) and Gregoriadis, Liposome Technology vols. I to III (2nd ed. 1993).

[0070] The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient that are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0071] Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above,

as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

[0072] For topical administration, the present compounds may be applied in liquid form. Compounds often are administered as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid. Examples of useful dermatological compositions used to deliver compounds to the skin are known (see, *e.g.*, Jacquet, *et al.* (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith, *et al.* (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

[0073] Compounds may be formulated with a solid carrier, which include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

[0074] Generally, the concentration of the compound in a liquid composition often is from about 0.1 wt% to about 25 wt%, sometimes from about 0.5 wt% to about 10 wt%. The concentration in a semi-solid or solid composition such as a gel or a powder often is about 0.1 wt% to about 5 wt%, sometimes about 0.5 wt% to about 2.5 wt%. A compound composition may be prepared as a unit dosage form, which is prepared according to conventional techniques known in the pharmaceutical industry. In general terms, such techniques include bringing a compound into association with pharmaceutical carrier(s) and/or excipient(s) in liquid form or finely divided solid form, or both, and then shaping the product if required. The compound composition may be formulated into any dosage form, such as tablets, capsules, gel capsules, liquid syrups, soft gels,

suppositories, and enemas. The compositions also may be formulated as suspensions in aqueous, non-aqueous, or mixed media. Aqueous suspensions may further contain substances which increase viscosity, including for example, sodium carboxymethylcellulose, sorbitol, and/or dextran. The suspension may also contain one or more stabilizers.

[0075] The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[0076] A useful compound dosage often is determined by assessing its *in vitro* activity in a cell or tissue system and/or *in vivo* activity in an animal system. For example, methods for extrapolating an effective dosage in mice and other animals to humans are known to the art (see, e.g., U.S. Pat. No. 4,938,949). Such systems can be used for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population) of a compound. The dose ratio between a toxic and therapeutic effect is the therapeutic index and it can be expressed as the ratio ED<sub>50</sub>/LD<sub>50</sub>. The compound dosage often lies within a range of circulating concentrations for which the ED<sub>50</sub> is associated with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compounds used in the methods described herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose sometimes is formulated to achieve a circulating plasma concentration range covering the IC<sub>50</sub> (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in *in vitro* assays, as such information often is used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0077] Another example of effective dose determination for a subject is the ability to directly assay levels of “free” and “bound” compound in the serum of the test subject. Such assays may utilize antibody mimics and/or “biosensors” generated by molecular imprinting techniques. The compound is used as a template, or “imprinting molecule”, to spatially organize polymerizable monomers prior to their polymerization with catalytic reagents. Subsequent removal of the imprinted molecule leaves a polymer matrix which contains a repeated “negative image” of the

compound and is able to selectively rebind the molecule under biological assay conditions (see, *e.g.*, Ansell, *et al.*, *Current Opinion in Biotechnology* (1996) 7:89-94 and in Shea, *Trends in Polymer Science* (1994) 2:166-173). Such “imprinted” affinity matrixes are amenable to ligand-binding assays, whereby the immobilized monoclonal antibody component is replaced by an appropriately imprinted matrix (see, *e.g.*, Vlatakis, *et al.*, *Nature* (1993) 361:645-647). Through the use of isotope-labeling, “free” concentration of compound can be readily monitored and used in calculations of  $IC_{50}$ . Such “imprinted” affinity matrixes can also be designed to include fluorescent groups whose photon-emitting properties measurably change upon local and selective binding of compound. These changes can be readily assayed in real time using appropriate fiberoptic devices, in turn allowing the dose in a test subject to be quickly optimized based on its individual  $IC_{50}$ . An example of such a “biosensor” is discussed in Kriz, *et al.*, *Analytical Chemistry* (1995) 67:2142-2144.

[0078] Exemplary doses include milligram or microgram amounts of the compound per kilogram of subject or sample weight, for example, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram. It is understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid described herein, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

[0079] The following examples are offered to illustrate but not to limit the invention.

### Examples

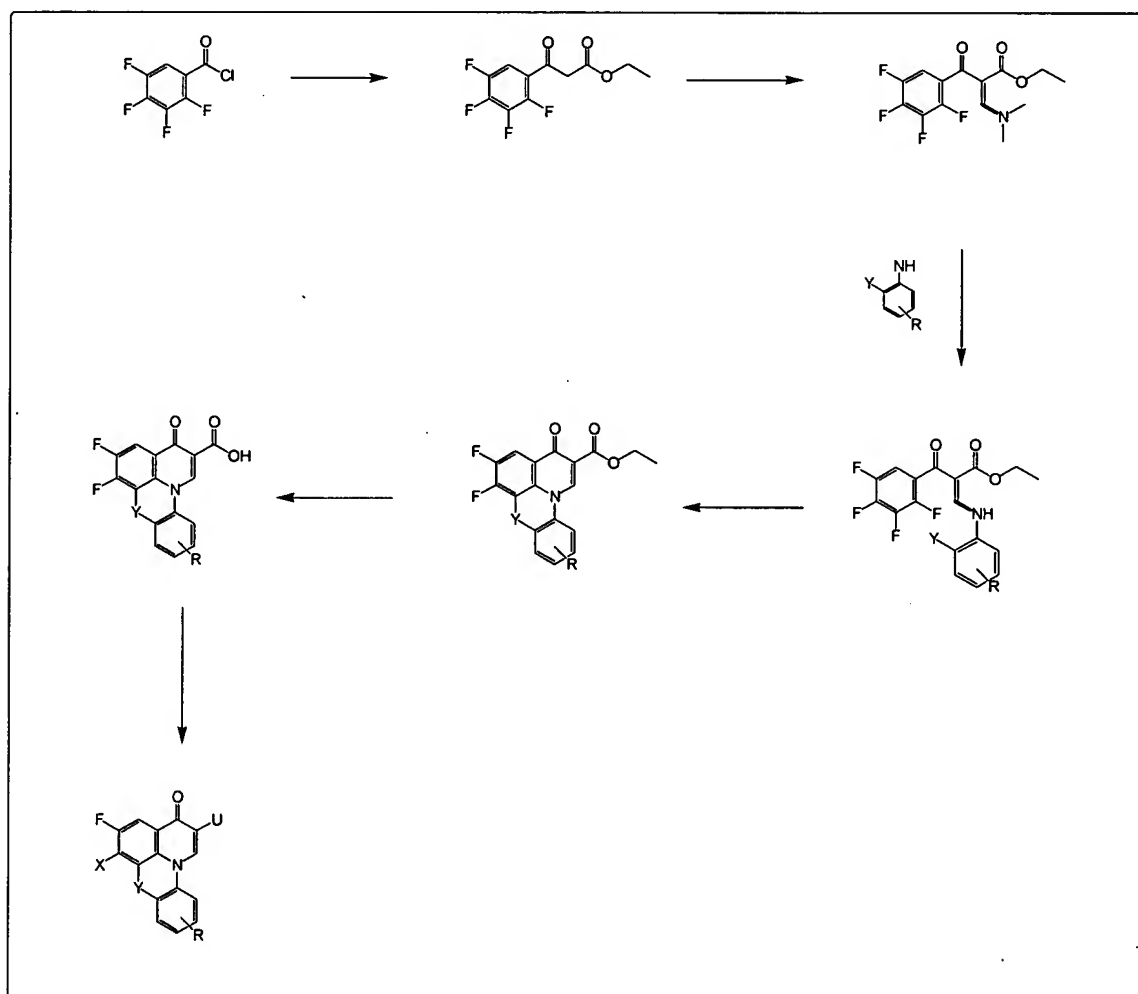
[0080] The following are exemplary procedures for synthesizing substituted quinobenzoxazines analogs.

#### Example 1

##### Preparation of Substituted Quinobenzoxazine Analogs

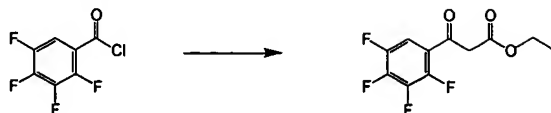
[0081] The general synthetic scheme for the preparation of substituted quinobenzoxazines analogs is shown in Scheme 1.

**Scheme 1**





Ethyl-(2',3',4',5'-tetrafluorobenzoyl)-ethanoate



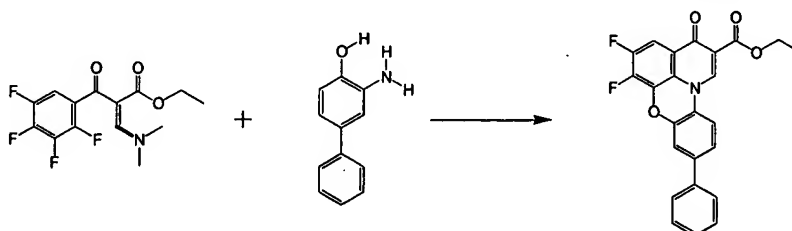
[0082] Potassium ethyl malonate (3.66 g, 21.5 mmol),  $\text{MgCl}_2$  (2.44 g, 25.7 mmol) and TEA (2.05 g, 20.3 mmol) were mixed in acetonitrile (70 ml) at 10-15°C for 2.5 hr. 2,3,4,5-tetrafluorobenzoyl chloride (2.00g, 10.3 mmol) in acetonitrile (10 ml) was added at 0°C over 15 min followed by a second addition of TEA (0.23g, 2.3 mmol). After allowing to warm to RT, the mixture was stirred for 16 hr. After removal of volatiles *in vacuo* Toluene (30 ml) was added and removed *in vacuo*. Following the addition of toluene (60 ml), HCl 1.5 M (40 ml) was added cautiously, ensuring the temperature did not exceed 25°C. The organic fraction was washed with HCl 1.5 M (2 x 25 ml) and water (2 x 25 ml), dried over  $\text{MgSO}_4$  and reduced to a light orange oil *in vacuo* ( $[\text{M}+1]^+$  265, 98%).

Ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(dimethylamino)-prop-2-enoate



[0083] Dimethyl acetal dimethyl formamide (0.61g, 5.1 mmol) was added dropwise to ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-ethanoate (0.9 g, 3.41 mmol) dissolved in acetic anhydride (2 ml), under argon. After 30 min solvent was removed *in vacuo* to leave the product as an orange oil in a quantitative yield ( $[\text{M}+1^+]$  320).

Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-k]l-8-phenyl-phenoxazine-5-carboxylate

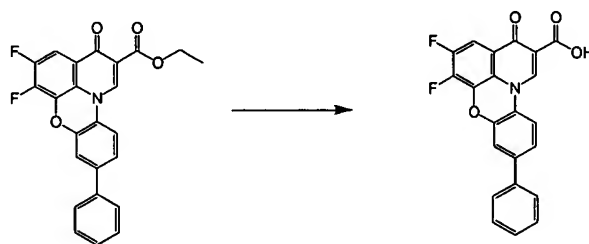


[0084] Ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(dimethylamino)-prop-2-enoate (3.4 g, 8.0 mmol) and 2-amino-4-phenyl-phenol (1.5g, 8.0 mmol) in 20 DMSO (20 ml) was stirred under

vacuum at 60°C for 30 min. K<sub>2</sub>CO<sub>3</sub> (5g) and MeCN (20 ml) was added and the suspension was heated at 80°C for 1 hr. After cooling to RT, the mixture was poured into a slight excess of dilute sulfuric acid and filtered. The product was recovered as a yellow-brown solid ([M+1]<sup>+</sup> 420, 65%).

### Example 2

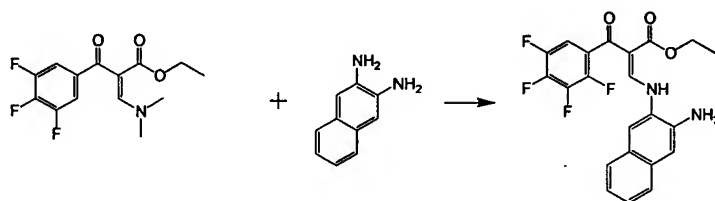
#### Preparation of 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-phenyl-phenoxazine-5-carboxylic acid



[0085] Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-phenyl-phenoxazine-5-carboxylate (2.2g, 5.3 mmol) was refluxed in a mixture of conc. HCl and acetic acid (20 ml each) for 2 hr. After cooling to room temperature cold water (40 ml) was added to the reaction mixture and the resulting precipitate filtered and washed with ether to afford the product as a yellow-brown solid 90% ([M+1]<sup>+</sup> 392).

### Example 3

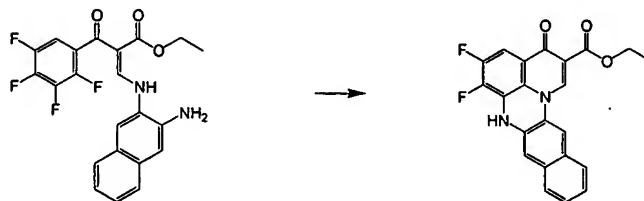
#### Preparation of Ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(naphthyl-2'', 3''-diamino)-prop-2-enoate



[0086] Ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(dimethylamino)-prop-2-enoate (10.53 g, 33 mmol) in acetonitrile (50 ml) was added to a solution of 2,3-diaminonaphthalene (5.22 g, 33 mmol) in acetonitrile (150 ml), maintained at 50°C under argon. After 3 hours, volatiles were removed *in vacuo* and the residue was subjected to chromatography over silica (15% EtOAc/Hexane) to yield the product as a yellow solid ([M+1]<sup>+</sup> 433) (55%).

#### Example 4

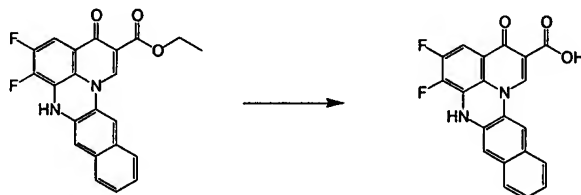
##### Preparation of Ethyl 1,2-Difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]benzo[*g*]-phendiazine-5-carboxylate



[0087] Ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(naphthyl-2'', 3'' diamino)-prop-2-enoate (600 mg 1.4 mmol) was dissolved in a slurry of  $K_2CO_3$  in DMF (500 ml). The mixture was stirred vigorously at 100°C for 1 hour, then allowed to cool to RT. The  $K_2CO_3$  was removed by filtration and the DMF removed *in vacuo* to leave a yellow-brown solid in quantitative yield. ( $[M+1]^+$  393).

#### Example 5

##### Preparation of 1,2-Difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]benzo[*g*]-phendiazine-5-carboxylic acid

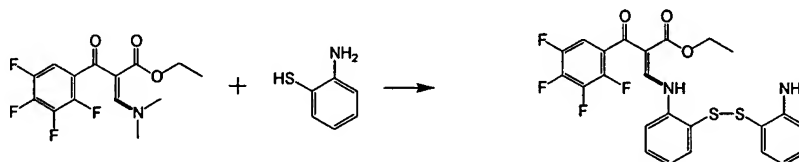


[0088] KOH solution (1N, 2.54 ml, 2.56 mmol) was added to a solution of ethyl 1,2-difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]benzo[*g*]-phendiazine-5-carboxylate (500 mg, 1.28 mmol) in ethanol (400 ml), heated under reflux. After 2 hours the reaction mixture was allowed to cool to RT, then neutralized with HCl solution (1N). The product was collected by filtration as a yellow solid, 89%. ( $[M+1]^+$  365).

### Example 6

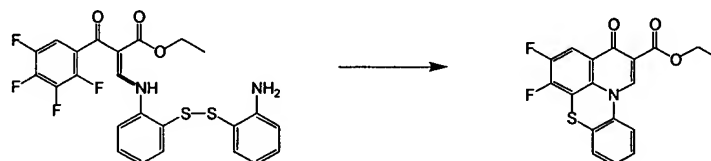
#### Preparation of Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-phenthiazine-5-carboxylate

##### Ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(N-aminobenzylidissulfide)-prop-2-enoate



[0089] Ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(dimethylamino)-prop-2-enoate (17.7 g, 55.3 mmol) in acetonitrile (10 ml) was added to a solution of 1,2-aminothiophenol dimer (5.22 g, 33 mmol) in acetonitrile (100 ml). After 3 hours, volatiles were removed *in vacuo* and the residue was subjected to chromatography over silica (1% MeOH/DCM) to yield the product as a yellow solid ( $[M+1]^+$  523) (50%).

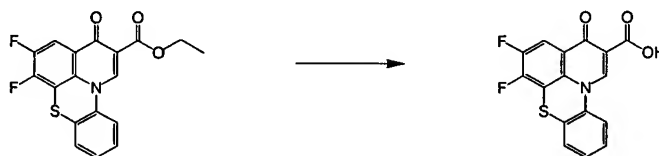
##### Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-phenthiazine-5-carboxylate



[0090] Ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(N-aminobenzylidissulfide)-prop-2-enoate (2.5 g 3.2 mmol) was dissolved in DMF (120 ml) and heated under reflux for six hours. Removal of DMF *in vacuo* gave the product as a yellow solid 90% ( $[M+1]^+$  360).

### Example 7

#### Preparation of 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-phenthiazine-5-carboxylic acid



[0091] KOH solution (1N, 3.0, 3.0 mmol) was added to a solution of ethyl 1,2-difluoro-4-oxo-4H-pyrido[3,2,1-kl]-phenthiazine-5-carboxylate (1000 mg, 2.5 mmol) in ethanol (400 ml), heated under reflux. After 2 hours the reaction mixture was allowed to cool to RT, then

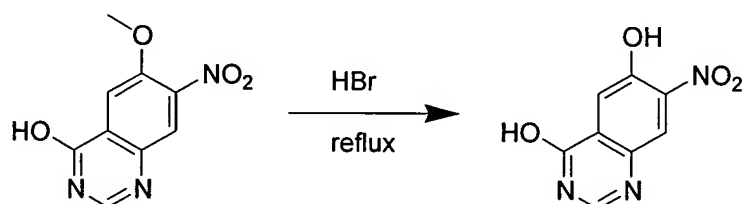
neutralized with HCl solution (1N). The product was collected by filtration as a yellow solid, ([M+1]<sup>+</sup> 332, 95%)

### Example 8

#### Preparation of

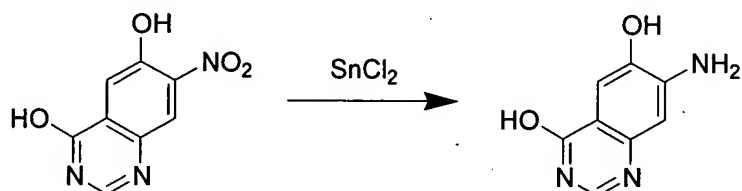
#### 5,6-Difluoro-9-hydroxy-3-oxo-3H-pyrido[3,2,1-kl]pyrimido[g]phenoxazine-2-carboxylic acid

##### 7-nitroquinazoline-4,6-diol



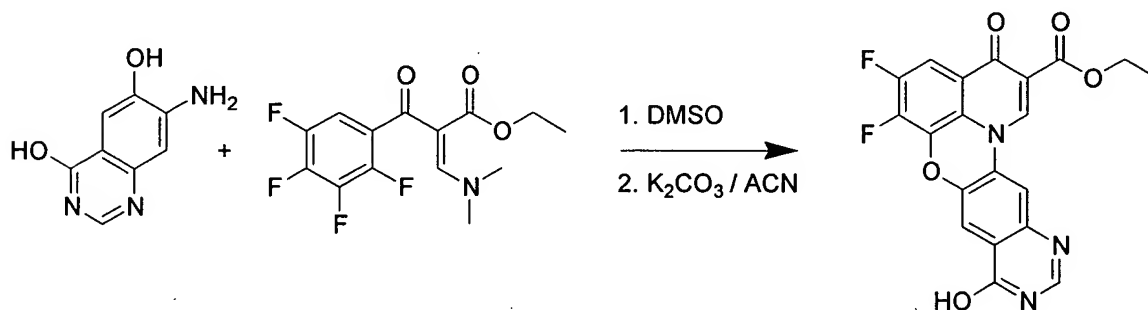
[0092] To a solution containing 20 ml of 48% aqueous HBr and 20 ml of AcOH was added 6-methoxy-7-nitro-3,4-dihydroquinazolin-4-one (1.4 g, 6.3 mmol) and the mixture was refluxed overnight. The resulting solution was evaporated to afford the crude phenol as a residue and was used without further purification (1.2 g, 5.8 mmol) (M+1, 208).

##### 7-aminoquinazoline-4,6-diol



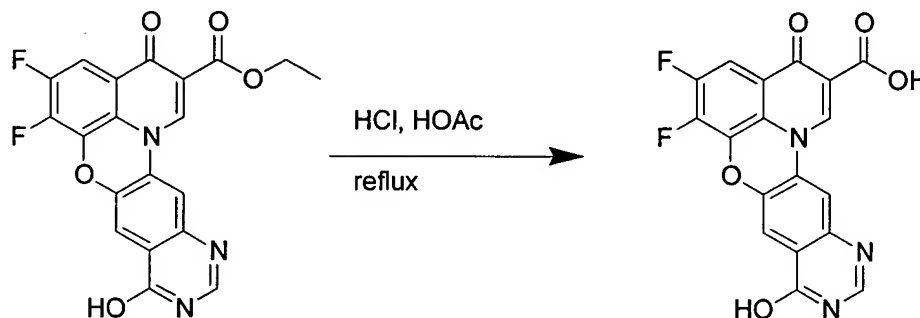
[0093] The crude product from above (1.0 g, 5.8 mmol) was diluted with 40 ml water and 3 g of Tin II chloride dihydrate was added and the reaction was stirred at room temperature. After 1h the reaction was neutralized with K<sub>2</sub>CO<sub>3</sub>, and extracted with EtOAc (3 X 50 mL). The combined organic extracts were dried over sodium sulfate and the solvent was removed *in vacuo* to afford the crude amino alcohol (1.0 g, 5.6 mmol) (M+1, 178).

Ethyl; 5,6-difluoro-9-hydroxy-3-oxo-3H-pyrido[3,2,1-kl]pyrimido[g]phenoxazine-2-carboxylate



[0094] To a solution of the tetrafluoroenamine (2.2 g, 6.9 mmol) in DMSO (3 mL) was added the aminophenol (1.0 g, 5.6 mmol) and the reaction mixture was stirred under vacuum (rotary evaporator) at 60°C for 20 minutes. The reaction mixture was allowed to cool to room temperature and was diluted with acetonitrile (200 mL) and potassium carbonate was added. The mixture was heated to reflux for 5 hours and poured into dilute HOAc/water. The solid product was collected by vacuum filtration and dried to afford the difluoroester as a tan solid (1.3g, 3.2 mmol) (M+1, 412).

5,6-Difluoro-9-hydroxy-3-oxo-3H-pyrido[3,2,1-kl]pyrimido[g]phenoxazine-2-carboxylic acid



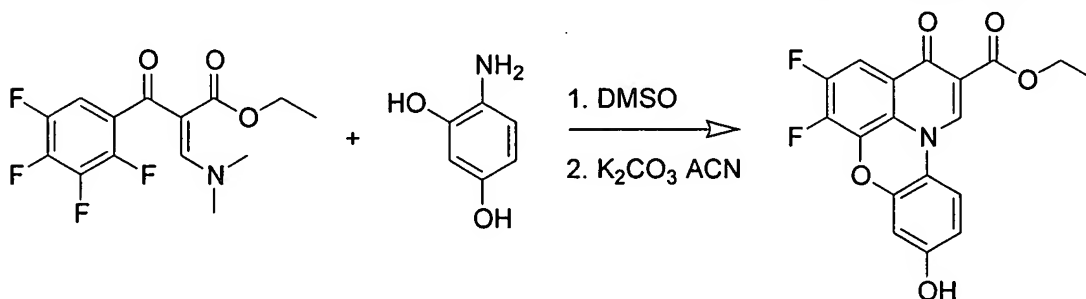
[0095] The difluoroester (1.3 g, 3.2 mmol) was dissolved in a 1:1 mixture of glacial acetic acid and 12 M HCl (20 mL) and refluxed for 30 min. The mixture was then cooled to room temperature and poured into water. The solid product was then collected by vacuum filtration and dried to afford the difluoroacid as a tan solid (0.98g, 2.5 mmol) ([M+1]<sup>+</sup> 392).

Example 9

Preparation of

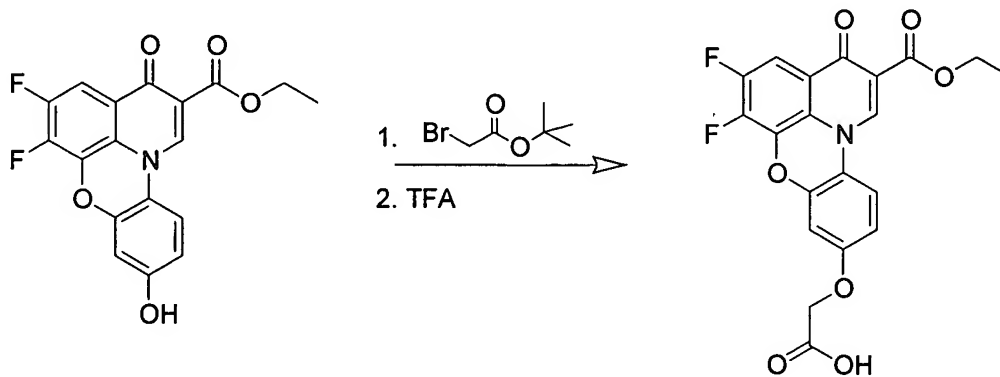
2-(2-(Ethoxycarbonyl)-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazin-9-yloxy)acetic acid

Ethyl 5,6-difluoro-9-hydroxy-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylate



[0096] To a solution of the tetrafluoroenamine (5.8 g, 18.2 mmol), dissolved in DMSO (12 mL), was added 2,4-dihydroxyaniline hydrochloride (2.5 g, 15.5 mmol) and the mixture was heated to 60°C under vacuum (rotary evaporator) for 20 minutes. The reaction mixture was then diluted with acetonitrile (100 mL) and potassium carbonate (3 g) was added and the mixture was refluxed overnight. The mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. A slight excess of 2 M HCl was added to rapidly dissolve the carbonate, and the solid precipitate was filtered and dried to afford the difluoroester as a tan solid (5.0 g, 13.9 mmol) (M+1, 360).

2-(2-(Ethoxycarbonyl)-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazin-9-yloxy)acetic acid

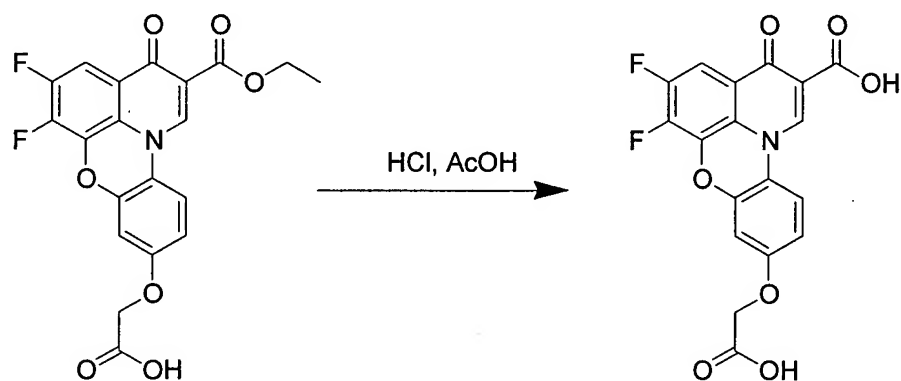


[0097] To a solution of the difluoroester (2.1 g, 5.8 mmol) and *tert*-butylbromoacetate (2.0 g, 10.3 mmol) in DMF (30 mL) was added potassium carbonate (2.0 g) and the mixture was heated to 60°C for 1 hour. The reaction was allowed to cool and poured into water (500 mL) and extracted with ethyl acetate (3 X 100 mL), washed with brine, dried over magnesium sulfate and filtered over a pad of silica gel (30 X 50 mm), eluting with ethyl acetate. The solvent was removed *in vacuo* and the resulting material was triturated with hexanes and dried to afford the *tert*-butyl ester as a tan solid (2.8 g, 5.8 mmol). This material was dissolved in trifluoroacetic acid (40 mL) and stirred at room temperature for 30 minutes. The solvent was removed *in vacuo* to afford the acid as a tan solid (2.4 g, 5.7 mmol) (M+1, 418).

### Example 10

#### Preparation of

#### 9-(Carboxymethoxy)-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylic acid

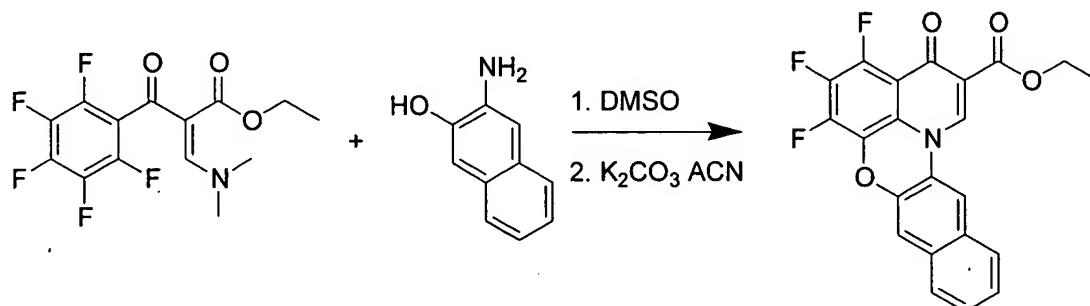


[0098] The difluoroester (2.4 g, 5.7 mmol) was dissolved in a 1:1 mixture of glacial acetic acid and 12 M HCl (40 mL) and refluxed for 1 hour. The mixture was then cooled to room temperature and poured into water. The solid product was then collected by vacuum filtration and dried to afford the difluoroacid as a tan solid (2.0 g, 5.1 mmol) (M+1, 390).



### Example 11

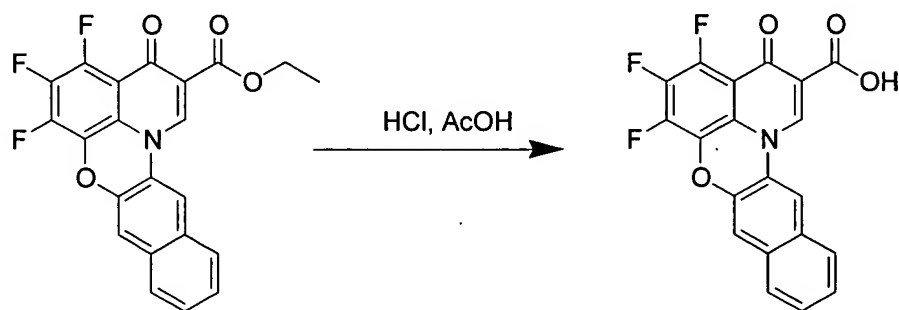
#### Preparation of Ethyl 1,2,3-trifluoro-4-oxo-4*H*-pyrido[3,2,1-kl]benzo[g]-phenoxazine-5-carboxylate



[0099] To a solution of pentafluoroenamine (8 g, 23.7 mmol), prepared by a similar procedure as for the tetrafluoroenamine dissolved in DMSO (12 mL) was added 3-amino-2-naphthol (3.5 g, 21.9 mmol) and the mixture was heated to 60°C under vacuum (rotary evaporator) for 2 hours. The reaction mixture was then diluted with acetonitrile (200 mL) and potassium carbonate (8.0 g) was added and the mixture was refluxed overnight. The mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. A slight excess of 2 M HCl was added to rapidly dissolve the carbonate, and the solid precipitate was filtered and dried to afford the difluoroester as a tan solid (1.3 g, 3.2 mmol) (M+1, 412).

### Example 12

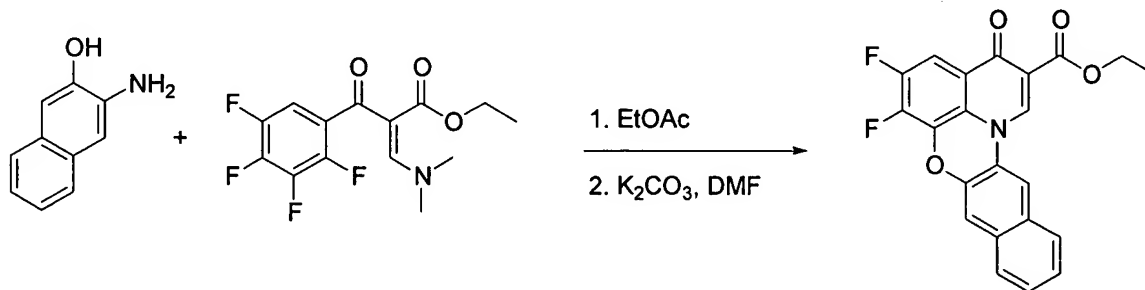
#### Preparation of 1,2,3-Trifluoro-4-oxo-4*H*-pyrido[3,2,1-kl]benzo[g]-phenoxazine-5-carboxylic acid



[0100] The trifluoroester (1.3 g, 3.2 mmol) was dissolved in acetic acid (5 mL) and 12 M HCl was added (5 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the trifluoroacid as a pale solid (1.0 g, 2.6 mmol) (M+1, 384).

### Example 13

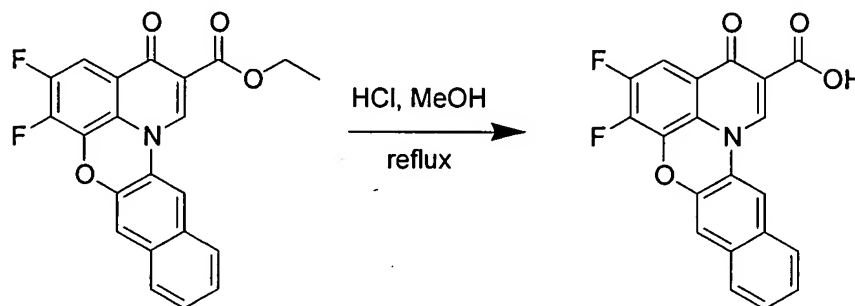
#### Preparation of Ethyl 1,2-difluoro-4-oxo-4*H*-pyrido[3,2,1-kl]benzo[g]-phenoxazine-5-carboxylate



[0101] To a solution of the enamine (30 g, 94 mmol) in ethyl acetate (100 mL) was added 3-amino-2-naphthol (10 g, 63 mmol) at room temperature and the mixture was immediately placed on a rotary evaporator and the solvent was removed over 2 hours at a temperature below 0°C (ice formed on the flask) to produce a yellow solid. To this solid was added ether (200 mL) and the slurry was filtered to afford a yellow solid. This solid was then dissolved in DMF (200 mL) and potassium carbonate was added (16.5 g, 120 mmol) and the mixture was heated to 90°C for 1 hour. The mixture was allowed to cool to room temperature and water was added (500 mL) and the resulting solid was filtered, washed with water and dried to afford the difluoroester as a tan solid (12.2 g, 30.8 mmol) (M+1, 394).

### Example 14

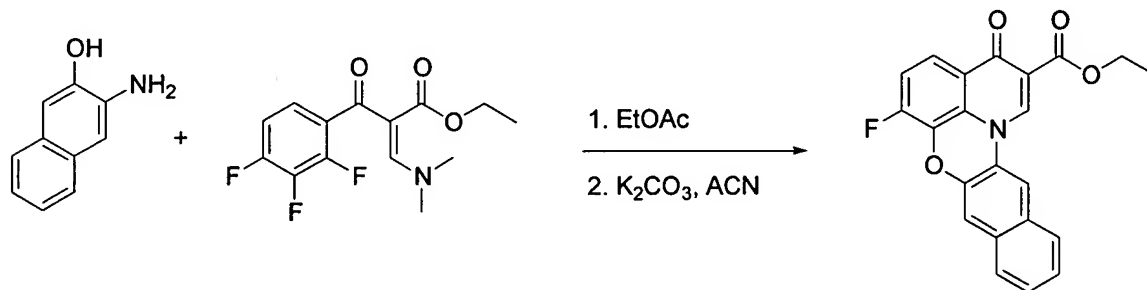
#### Preparation of 1,2-Difluoro-4-oxo-4*H*-pyrido[3,2,1-kl]benzo[g]-phenoxazine-5-carboxylic acid



[0102] The difluoroester (5 g, 12.7 mmol) was dissolved in methanol (50 mL) and *conc* HCl was added (20 mL) and the mixture was refluxed for 12 hours. The mixture was allowed to cool to room temperature and the solid was collected by vacuum filtration, washing with methanol to afford the difluoroacid as a light tan powder (3.6 g, 9.9 mmol) (M+1, 366).

### Example 15

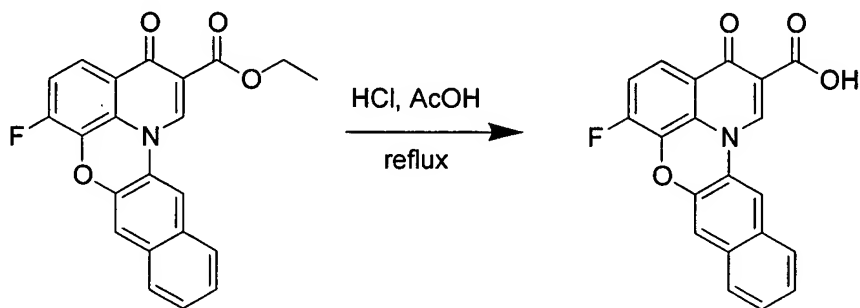
#### Preparation of Ethyl 1-fluoro-4-oxo-4*H*-pyrido[3,2,1-kl]benzo[g]-phenoxazine-5-carboxylate



[0103] To a solution of the enamine, similarly prepared as the tetrafluoroenamine (14 g, 46.3 mmol) in ethyl acetate (100 mL) was added 3-Amino-2-naphthol ( 5.0 g, 31.2 mmol) at room temperature and the mixture was immediately placed on a rotary evaporator and the solvent was removed over 2 hours at a temperature below 0°C (ice formed on the flask) to produce a yellow solid. To this solid was added methanol (200 mL) and the slurry was filtered to afford a yellow solid. This solid was then dissolved in acetonitrile (200 mL) and potassium carbonate was added (10.0 g, 72.5 mmol) and the mixture was heated to 80°C for 1 hour. The mixture was allowed to cool to room temperature and water was added (500 mL) and the resulting solid was filtered, washed with water and dried to afford the fluoroester as a tan solid (6.0 g, 16.0 mmol) (M+1, 376).

### Example 16

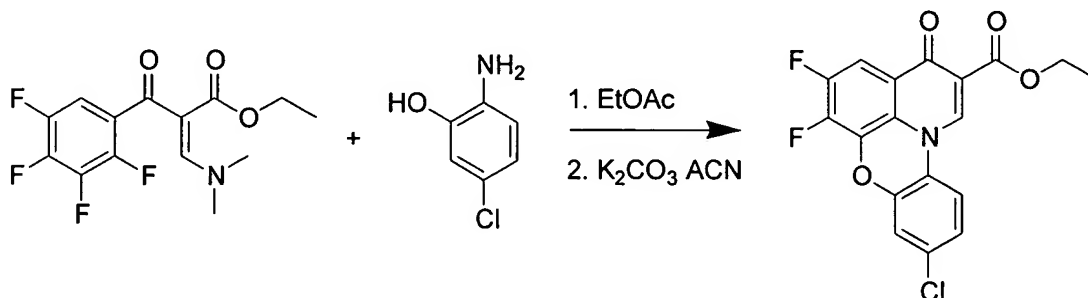
#### Preparation of 1-Fluoro-4-oxo-4*H*-pyrido[3,2,1-kl]benzo[g]-phenoxazine-5-carboxylic acid



[0104] The fluoroester (6.0 g, 16.0 mmol) was dissolved in acetic acid (10 mL) and 12 M HCl was added (10 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the fluoroacid as a pale solid (4.8 g, 13.8 mmol) (M+1, 348).

Example 17

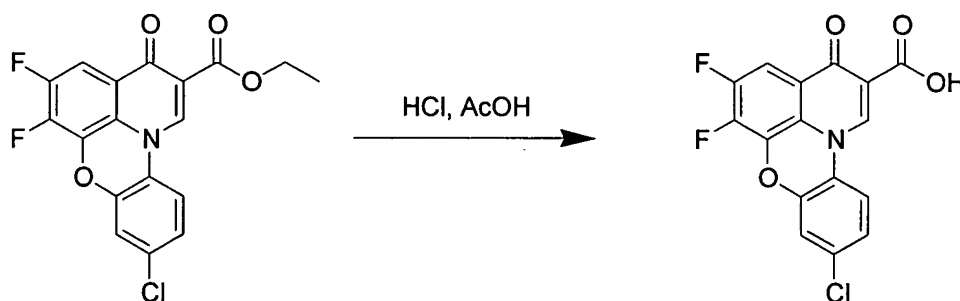
Preparation of Ethyl 9-chloro-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylate



[0105] To a solution of the enamine (14.4 g, 45.3 mmol) in ethyl acetate (200 mL) was added 5-chloro-2-aminophenol (5.0 g, 34.8 mmol) and the solvent was removed *in vacuo* with a rotary evaporator over 2 hours without heating. Methanol was added and the resulting phenolic enamine was isolated by vacuum filtration. The resulting solid (7.0 g) was dissolved in acetonitrile and potassium carbonate was added and the resulting mixture was heated to reflux for 2 hours. The mixture was then allowed to cool to room temperature and poured into Dilute HCl. The resulting solid was collected by vacuum filtration and dried to afford the difluoroester as a pale yellow solid (5.0 g, 13.3 mmol) (M+1, 378).

Example 18

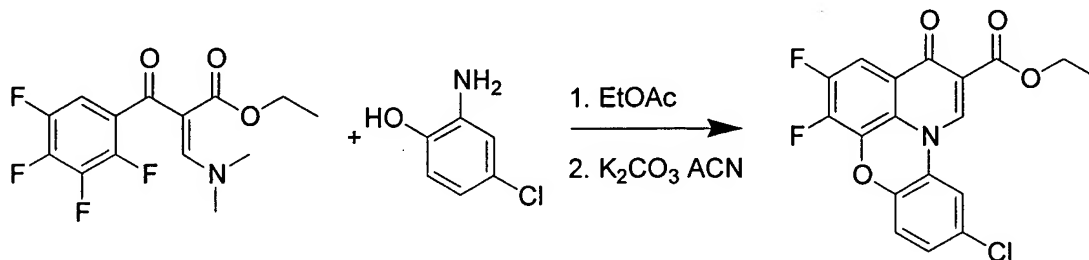
Preparation of 9-Chloro-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylic acid



[0106] The difluoroester (5.0 g, 13.3 mmol) was dissolved in acetic acid (45 mL) and 12 M HCl was added (30 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the difluoroacid as a pale solid (4.0 g, 10.6 mmol) (M+1, 350).

### Example 19

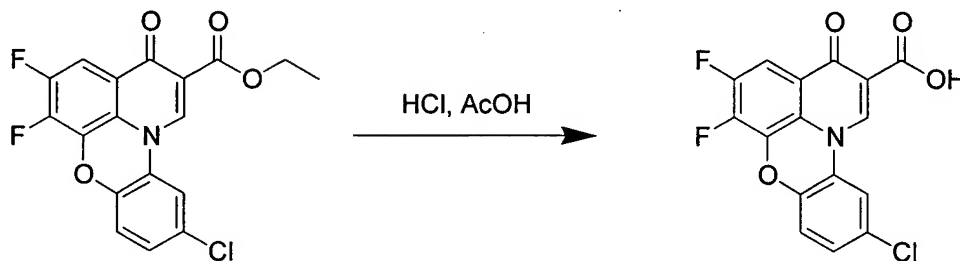
#### Preparation of Ethyl 10-chloro-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylate



[0107] To a solution of the enamine (14.4 g, 45.3 mmol) in ethyl acetate (200 mL) was added 4-chloro-2-aminophenol (5.0 g, 34.8 mmol) and the solvent was removed *in vacuo* with a rotary evaporator over 2 hours without heating. Methanol was added and the resulting phenolic enamine was isolated by vacuum filtration. The resulting solid (7.5 g) was dissolved in acetonitrile and potassium carbonate was added and the resulting mixture was heated to reflux for 2 hours. The mixture was then allowed to cool to room temperature and poured into Dilute HCl. The resulting solid was collected by vacuum filtration and dried to afford the difluoroester as a pale yellow solid (5.0 g, 13.3 mmol) (M+1, 378).

### Example 20

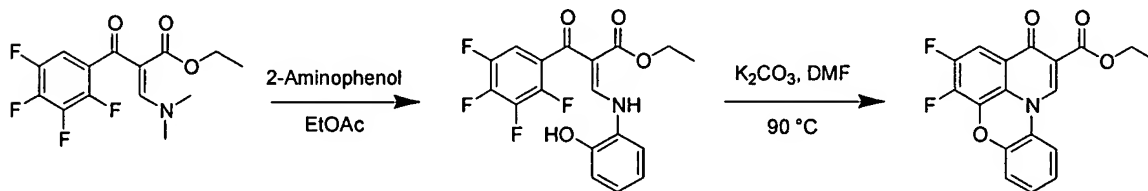
#### Preparation of 10-Chloro-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylic acid



[0108] The difluoroester (2.5 g) was dissolved in acetic acid (25 mL) and 12 M HCl was added (20 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the difluoroacid as a pale solid (2.0 g, 5.3 mmol) (M+1, 350).

### Example 21

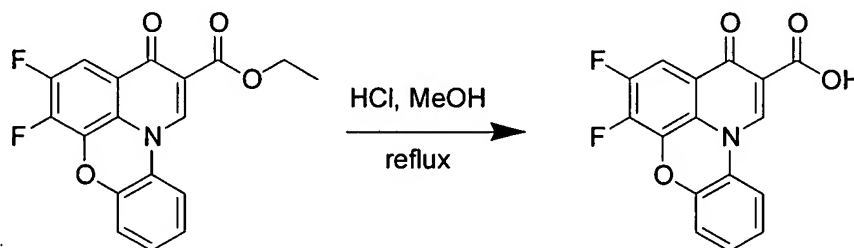
#### Preparation of Ethyl 5,6-Difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylate



[0109] To a solution of the enamine (5.7 g, 17.9 mmol) in ethyl acetate (50 mL) was added 2-aminophenol (1.9 g, 17.43 mmol) at room temperature and the mixture was immediately placed on a rotary evaporator and the solvent was removed over 2 hours at a temperature below 0°C (ice formed on the flask) to produce a yellow solid. To this solid was added ether (25 mL) and the slurry was filtered to afford a yellow solid. This solid was then dissolved in DMF (20 mL) and potassium carbonate was added (2.9g, 21 mmol) and the mixture was heated to 90°C for 1 hour. The mixture was allowed to cool to room temperature and water was added (200 mL) and the resulting solid was filtered, washed with water and dried to afford the phenoxazine as a tan solid (2.9g, 8.45 mmol) (M+1, 344).

### Example 22

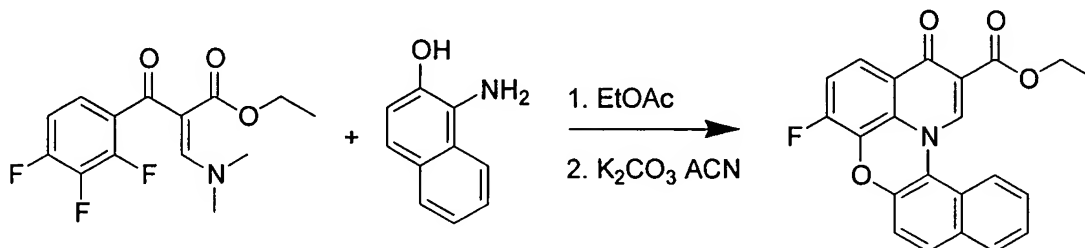
#### Preparation of 5,6-Difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylic acid



[0110] The difluoroester (5.0 g, 14 mmol) was dissolved in methanol (50 mL) and *conc* HCl was added (20 mL) and the mixture was refluxed for 2 hours. The mixture was allowed to cool to room temperature and the solid was collected by vacuum filtration, washing with methanol to afford the difluoroacid as a light tan powder (4.2 g, 13.3 mmol, 91%) (M+1,316).

Example 23

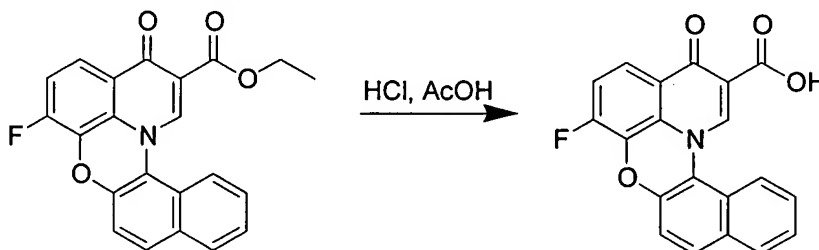
Preparation of Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]benzo[h]-phenoxazine-5-carboxylate



[0111] To a solution of the enamine (14.0 g, 45.3 mmol) in ethyl acetate (200 mL) was added 1-amino-2-naphthol (5.0 g, 31.3 mmol) and the solvent was removed *in vacuo* with a rotary evaporator over 2 hours without heating. Methanol was added and the resulting phenolic enamine was isolated by vacuum filtration. The solid was dissolved in acetonitrile and potassium carbonate (10 g) was added and the mixture was heated to reflux for 2 hours. The mixture was then allowed to cool to room temperature and poured into Dilute HCl. The resulting solid was collected by vacuum filtration and dried to afford the difluoroester as a pale yellow solid (5.0 g, 13.3 mmol) (M+1, 376).

Example 24

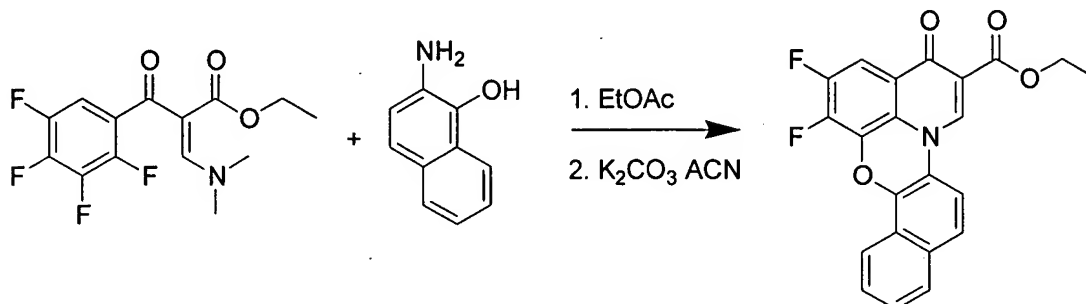
Preparation of 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]benzo[h]-phenoxazine-5-carboxylic acid



[0112] The difluoroester (5.5 g) was dissolved in acetic acid (25 mL) and 12 M HCl was added (20 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the difluoroacid as a pale solid (5.0 g, 14.4 mmol) (M+1, 348).

Example 25

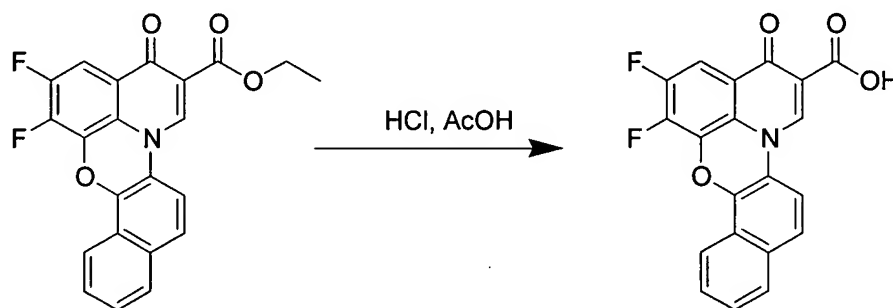
Preparation of Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-k]benzo[f]-phenoxazine-5-carboxylate



[0113] To a solution of the enamine (45 g, 141 mmol) in ethyl acetate (500 mL) was added 2-amino-1-naphthol (15.0 g, 93.8 mmol) and the solvent was removed *in vacuo* with a rotary evaporator over 2 hours without heating. Methanol was added and the phenolic enamine was isolated by vacuum filtration. The resulting solid was dissolved in acetonitrile (400 mL) and potassium carbonate (25 g) was added and the mixture was heated to reflux for 2.5 hours. The mixture was then allowed to cool to room temperature and poured into Dilute HCl. The resulting solid was collected by vacuum filtration and dried to afford the difluoroester as a pale yellow solid (19.69 g, 50.1 mmol) (M+1, 394).

Example 26

Preparation of 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-k]benzo[f]-phenoxazine-5-carboxylic acid



[0114] The difluoroester (15.0 g, 38.1 mmol) was dissolved in acetic acid (60 mL) and 12M HCl was added (60 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the difluoroacid as a pale solid (11.7 g, 32 mmol) (M+1, 366).

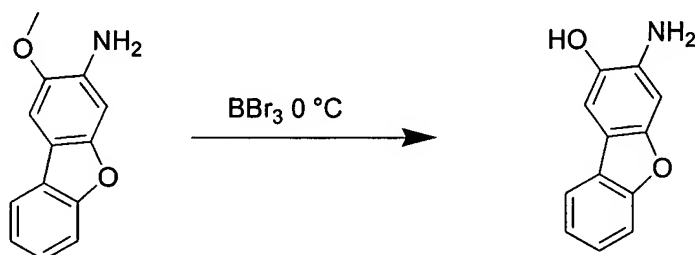


Example 27

Preparation of Ethyl

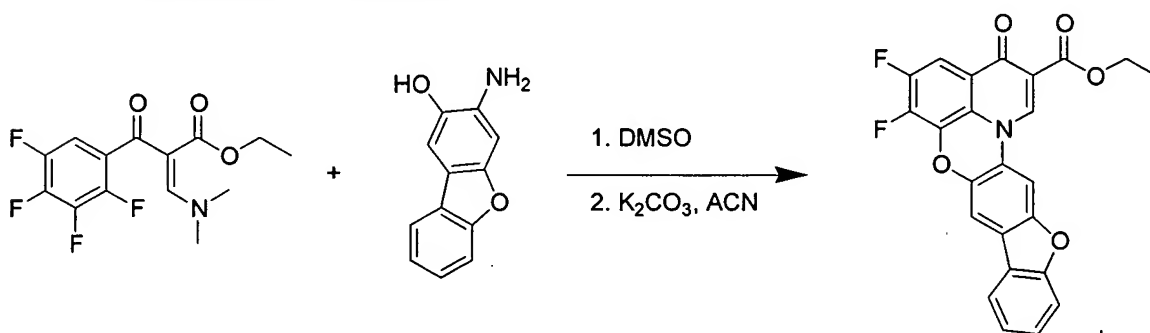
1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]benzo[b]furan[2,3-g]-phenoxazine-5-carboxylate

3-Aminodibenzofuran-2-ol



[0115] To a solution of the dibenzofuran (15 g, 70.4 mmol) dissolved in methylene chloride (500 mL) at 0°C was added BBr<sub>3</sub> (200 mL, 1 M in CH<sub>2</sub>Cl<sub>2</sub>) *via* addition funnel. After the addition was complete, the mixture was allowed to come to room temperature over 1 hour and then quenched with water followed by potassium carbonate (40 g). The resulting solid was recovered by vacuum filtration and dried to afford the hydroxyl dibenzofuran as a white solid (13.2 g, 199 mmol) (M+1, 200).

Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]benzo[b]furan[2,3-g]-  
phenoxazine-5-carboxylate



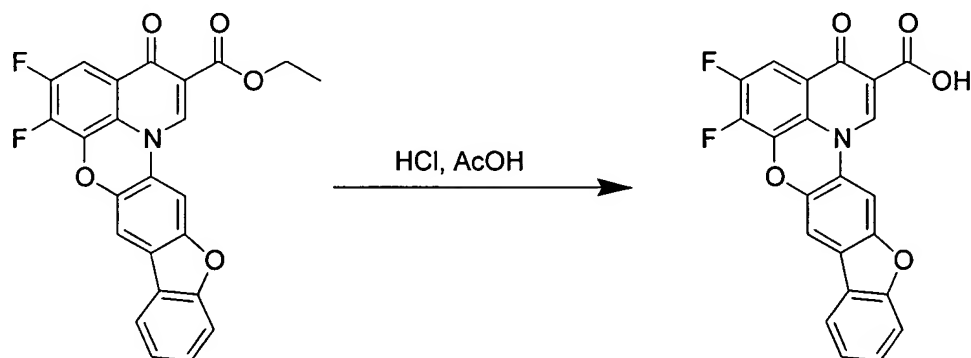
[0116] To a solution of the tetrafluoroenamine (15.0 g, 47 mmol) dissolved in DMSO (30 mL) was added the hydroxyl dibenzofuran (12.0 g, 60 mmol) and the mixture was heated to 60°C under vacuum (rotary evaporator) for 20 minutes. The reaction mixture was then diluted with acetonitrile (200 mL) and potassium carbonate (17 g) was added and the mixture was refluxed for 2.5 hours. The mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. A

slight excess of 2 M HCl was added to rapidly dissolve the carbonate, and the solid precipitate was filtered and dried to afford the difluoroester as a tan solid (15.0 g, 34.6 mmol) (M+1, 434).

### Example 28

#### Preparation of

#### 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]benzo[b]furan[2,3-g]-phenoxazine-5-carboxylic acid

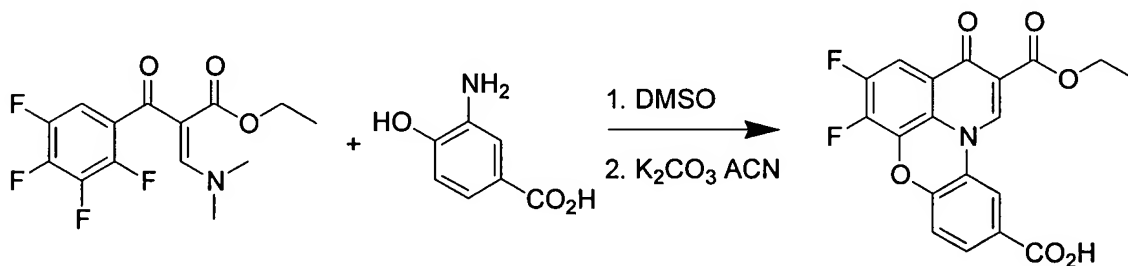


[0117] The difluoroester (15.0 g, 34.6 mmol) was dissolved in acetic acid (60 mL) and 12 M HCl was added (60 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the difluoroacid as a pale solid (13.7 g, 34 mmol) (M+1, 406).

### Example 29

#### Preparation of Ethyl

#### 2-(ethoxycarbonyl)-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-10-carboxylate



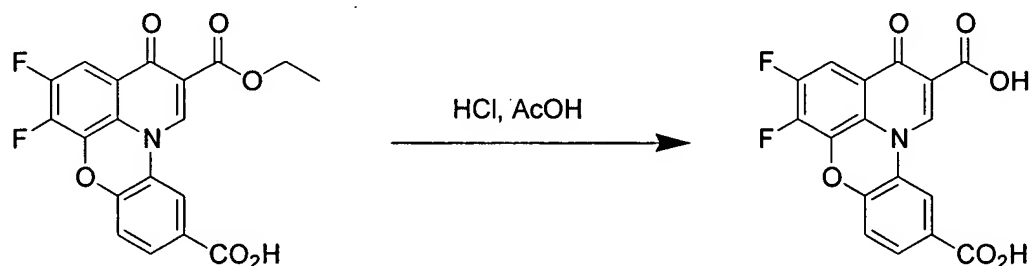
[0118] To a solution of the tetrafluoroenamine (7.0 g, 21.9 mmol) dissolved in DMSO (25 mL) was added 4-hydroxy-3-amino benzoic acid (3.0 g, 19.6 mmol) and the mixture was heated to 60°C under vacuum (rotary evaporator) for 2 hours. The reaction mixture was then diluted with

acetonitrile (200 mL) and potassium carbonate (8.0 g) was added and the mixture was refluxed overnight. The mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. A slight excess of 2 M HCl was added to rapidly dissolve the carbonate, and the solid precipitate was filtered and dried to afford the difluoroester as a tan solid (6.2 g, 16.0 mmol) (M+1, 388).

### Example 30

#### Preparation of

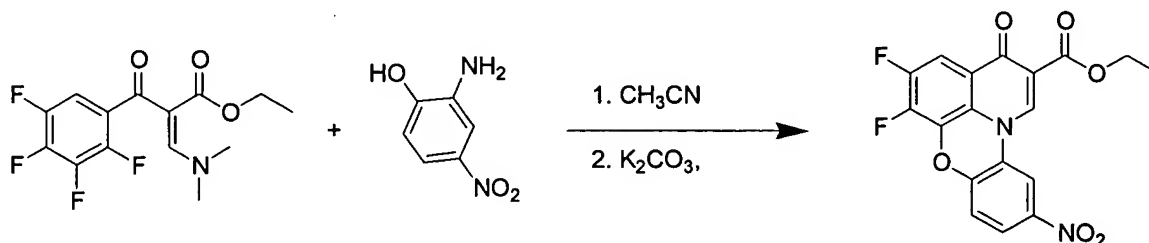
#### 2-(Ethoxycarbonyl)-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-10-carboxylic acid



[0119] The difluoroester (6.2, 16.0 mmol g) was dissolved in acetic acid (25 mL) and 12 M HCl was added (20 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the difluorodi-acid as a pale solid (5.3 g, 14.8 mmol) (M+1, 360).

### Example 31

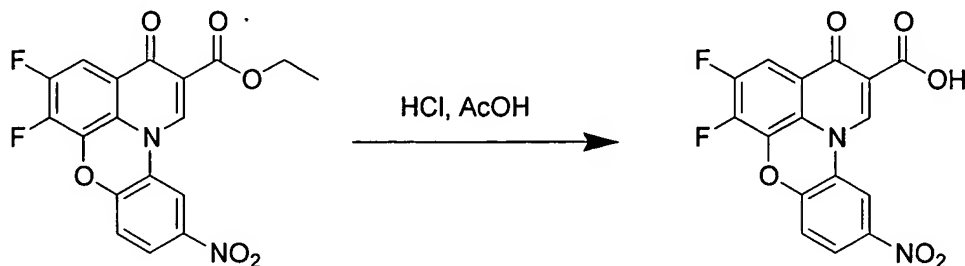
#### Preparation of Ethyl 5,6-difluoro-10-nitro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylate



[0120] A solution of the enamine (6.0 g, 18.7 mmol) and 2-amino-4-nitrophenol (3.5 g, 23.3 mmol) in acetonitrile was heated to 80°C for 15 minutes. Potassium carbonate was then added (8.0 g) and the mixture was heated to reflux overnight. The reaction mixture was then filtered hot and the solvent was removed *in vacuo* to afford the crude nitroester (5.0 g, 12.8 mmol) (M+1, 389).

Example 32

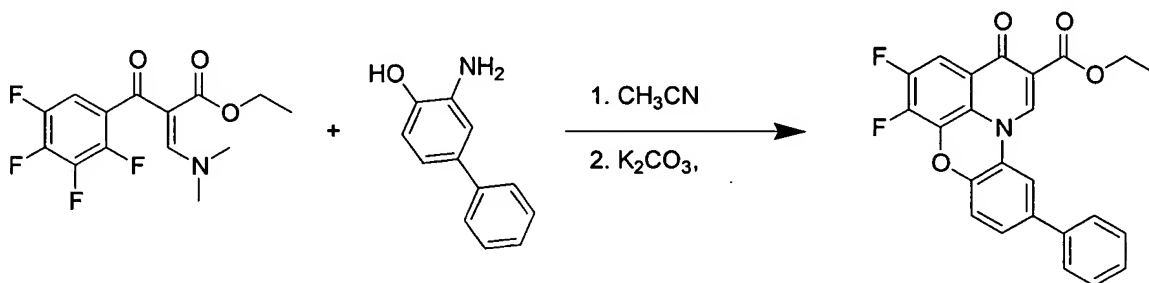
Preparation of 5,6-Difluoro-10-nitro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylic acid



[0121] The crude difluoroester (5.0 g, 12.8 mmol) was dissolved in acetic acid (25 mL) and 12 M HCl was added (20 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the difluoroacid as a pale solid (2.0 g, 5.5 mmol) (M+1, 361).

Example 33

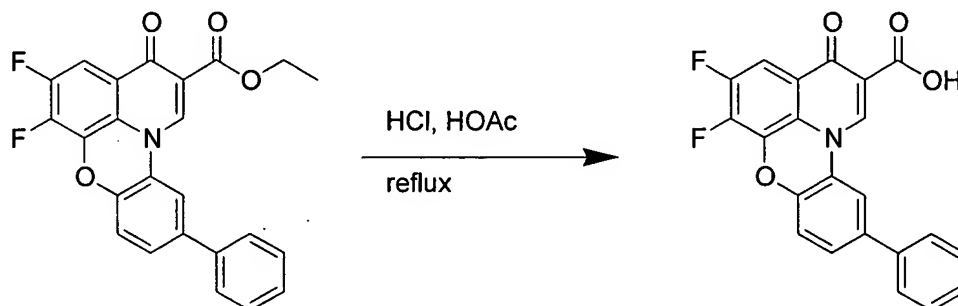
Preparation of Ethyl 5,6-difluoro-3-oxo-10-phenyl-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylate



[0122] A solution of the enamine (5.4 g, 16.9 mmol) and 3-amino-4-hydroxybiphenyl (3.5 g, 18.9 mmol) in acetonitrile was heated to 80°C for 90 minutes. Potassium carbonate was then added (8.0 g) and the mixture was heated to reflux overnight. The reaction mixture was then filtered hot and the solvent was removed *in vacuo* to afford the crude difluoroester (3.9 g, 9.3 mmol) (M+1, 420).

### Example 34

#### Preparation of 5,6-Difluoro-3-oxo-10-phenyl-3H-pyrido[3,2,1-kl]phenoxazine-2-carboxylic acid

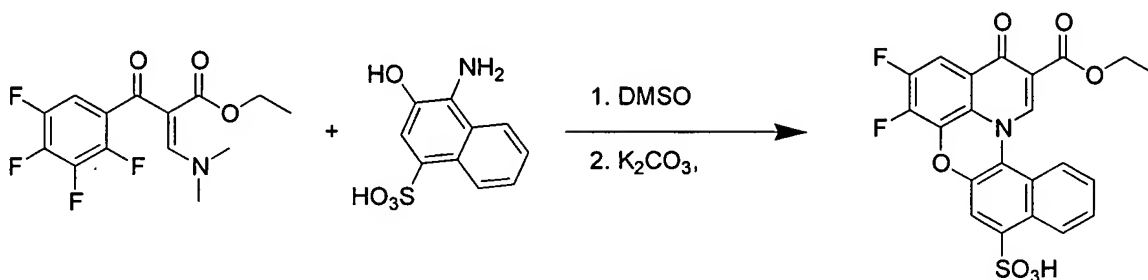


[0123] The crude difluoroester (3.6 g, 8.6 mmol) was dissolved in acetic acid (10 mL) and 12 M HCl was added (10 mL) and the reaction mixture was heated to reflux for 2 hours. The mixture was then cooled to room temperature, poured into water and the solid product was collected by vacuum filtration and dried to afford the difluoroacid as a pale solid (2.6 g, 6.6 mmol) (M+1,392).

### Example 35

#### Preparation of Ethyl

#### 1,2-Difluoro-4-oxo-4H-11-sulfonic-acid-pyrido[3,2,1-kl]benzo[h]-phenoxazine-5-carboxylate

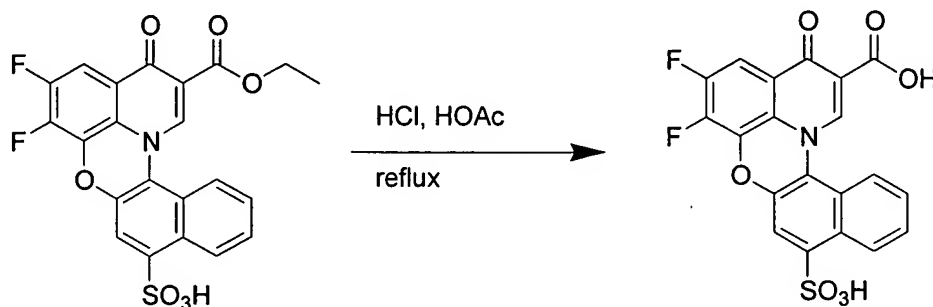


[0124] To a solution of the tetrafluoroenamine (5.4 g, 16.9 mmol) dissolved in DMSO (30 mL) was added 1-amino-2-hydroxy-4-naphthalenesulfonic acid (4.8 g, 20 mmol) and the mixture was heated to 60°C under vacuum (rotary evaporator) for 2 hours. To the reaction mixture was added potassium carbonate (10.0 g) and the mixture was heated to 60°C for 1 hour. The mixture was allowed to cool to room temperature and a slight excess of 2 M HCl was added to rapidly dissolve the carbonate. The aqueous layer was decanted and the remaining organic residue was dissolved in methanol (100 mL) and precipitated with ethyl acetate (200 mL) and the solid precipitate was filtered and dried to afford the sulfonic acid as a brown solid (3.1 g, 6.5 mmol) (M+1, 474).

Example 36

Preparation of

1,2-Difluoro-4-oxo-4H-11-sulfonic-pyrido[3,2,1-kl]benzo[h]-phenoxazine-5-carboxylic acids

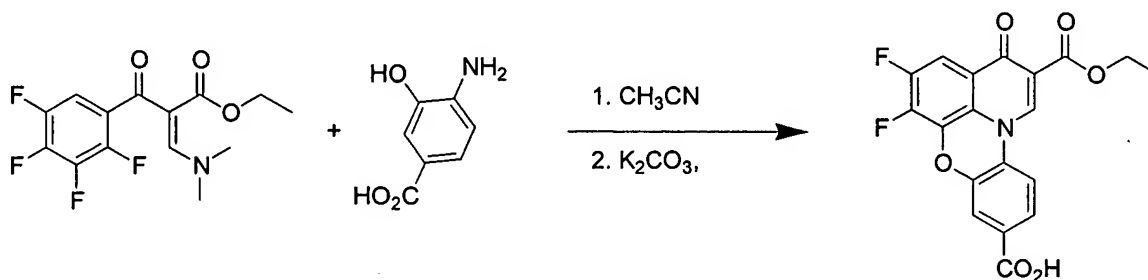


[0125] The crude difluoroester (1.5 g, 3.2 mmol) was dissolved in acetic acid (10 mL) and 12 M HCl was added (10 mL) and the reaction mixture was heated to reflux for 30 minutes. The solvent was removed *in vacuo* to afford the sulfonic acid as a brown solid (1.1 g, 2.5 mmol) (M+1, 446)

Example 37

Preparation of

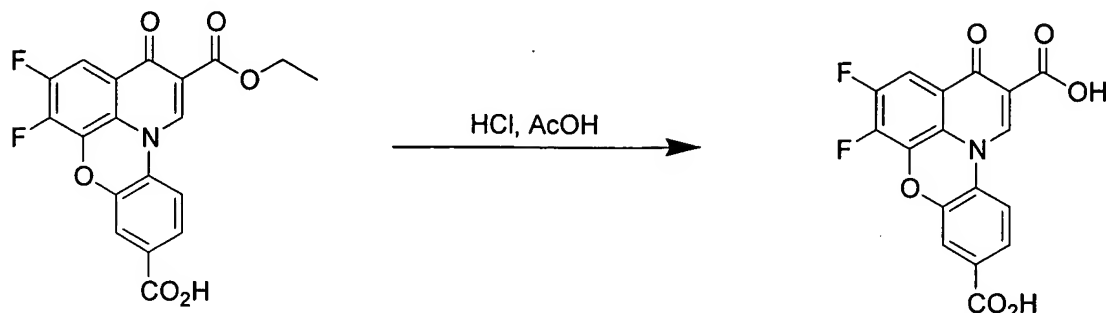
2-(Ethoxycarbonyl)-5,6-difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-9-carboxylic acid



[0126] A solution of the difluoroenamine (5.2 g, 16.3 mmol) and 4-amino-3-hydroxybenzoic acid (4.0 g, 26.1 mmol) in DMSO was stirred at room temperature for 1.5 hours. Potassium carbonate (8 g) was then added and the reaction mixture was stirred under vacuum (rotary evaporator) for 1 hour. The mixture was then heated to 100°C for 1 hour and then allowed to cool to room temperature. The reaction mixture was then poured into 1 M H<sub>2</sub>SO<sub>4</sub> (500 mL) and the solids were recovered by vacuum filtration. The resulting solid was dried to afford the crude difluoroacid as a tan solid (5.0 g, 12.9 mmol) (M+1, 388).

Example 38

Preparation of 5,6-Difluoro-3-oxo-3H-pyrido[3,2,1-kl]phenoxazine-2,9-dicarboxylic acid

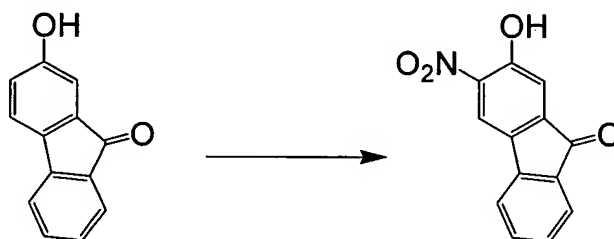


[0127] The crude difluoroester (5.0 g, 12.9 mmol) was dissolved in acetic acid (20 mL) and 12 M HCl was added (20 mL) and the reaction mixture was heated to reflux for 1 hour. The reaction was allowed to cool to room temperature and water was added. The resulting solid was collected by vacuum filtration and dried overnight to afford the di-acid as a tan solid (1.9g, 5.3 mmol) (M+1, 360).

Example 39

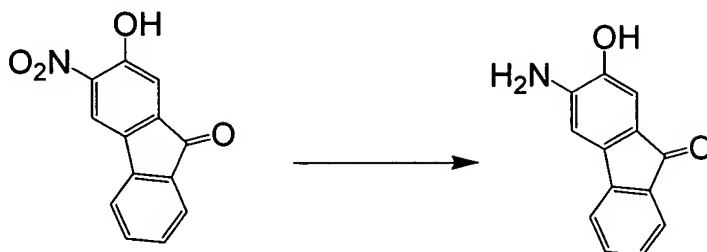
Preparation of Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-fluorenone-5-carboxylate

3-Nitro-2-hydroxyfluorenone



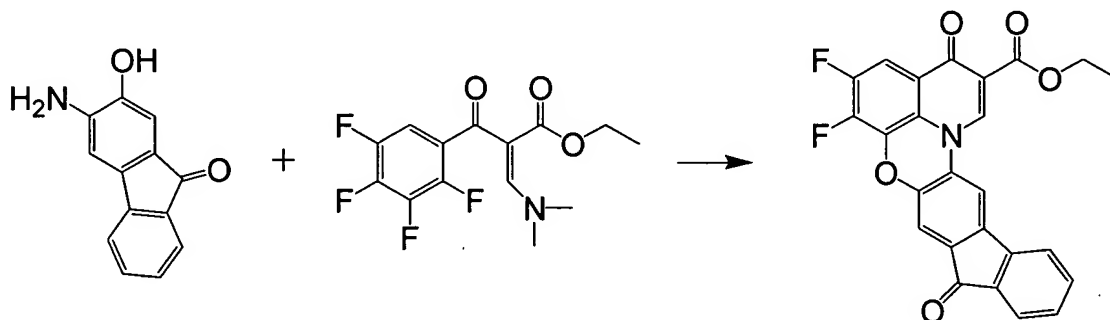
[0128] A solution of  $\text{NO}_2\text{BF}_4$  (3.52 g, 25.5 mmol) in acetonitrile (100 ml) was added dropwise to a solution of 2-hydroxyfluorenone (5 g, 25.5 mmol) in acetonitrile (400 ml) at ambient temperature. The reaction mixture was then cooled to  $0^\circ\text{C}$  and water (100 ml) was added to precipitate impurities. After filtration, water (200 ml) was added and the precipitate filtered off as a red solid (68%) (M+1, 242).

3-amino-2-hydroxyfluorenone



[0129] A mixture of 3-nitro-2-hydroxyfluorenone (1.6 g, 6.6 mmol) and  $\text{SnCl}_2$  (3 g, 6.6 mmol) was refluxed in 100 ml acetic acid:conc. HCl (1:1) for 1 hour. The mixture was allowed to cool to room temperature and neutralized with ammonium hydroxide. After extracting with EtOAc (3 x 100 ml), combined organic fractions were dried over magnesium sulfate and evaporated to leave the product as a brown solid (65%) (M+1, 212).

Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-fluorenone-5-carboxylate

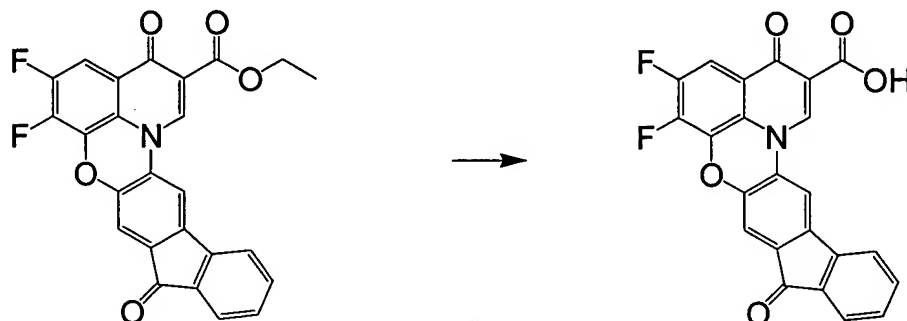


[0130] A mixture of 3-amino-2-hydroxyfluorenone (0.9 g, 4.26 mmol) and ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(dimethylamino)-prop-2-enoate (1.36 g, 4.26 mmol) were heated in DMSO (50 ml) under vacuum for 18 hr. The product was extracted using EtOAc/Brine and the organic layers combined and dried to give the product as a red solid. The solid was dissolved in DMSO (40 ml) containing a large excess of  $\text{K}_2\text{CO}_3$  and heated at  $100^\circ\text{C}$  for 30 min. After cooling to room temperature, brine (30 ml) was added and the precipitated product collected as a yellow solid (60% over two steps) (M+1, 446).



Example 40

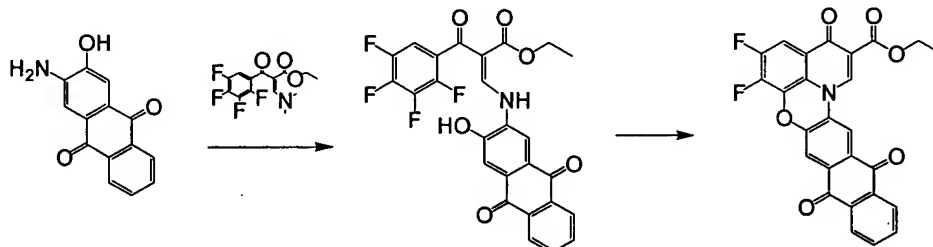
Preparation of 1,2-Difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]-8-fluorenone-5-carboxylic acid



[0131] A mixture of ethyl 1,2-difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]-8-fluorenone-5-carboxylate in acetic acid:conc. HCl (1:1) (50 ml each) was heated at reflux for 2 hr. After cooling to room temperature, water (50 ml) was added and the product collected as yellow solid (94%) (M+1, 418).

Example 41

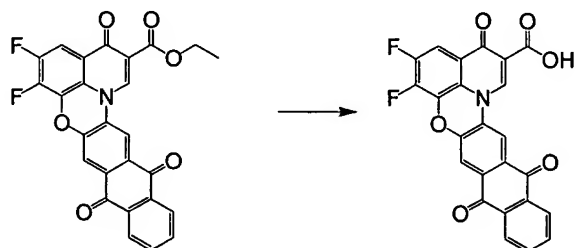
Preparation of Ethyl 1,2-Difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]-8-anthraquinone-5-carboxylate



[0132] A mixture of 3-amino-2-hydroxyanthraquinone (5.54 g, 23.2 mmol) and ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(dimethylamino)-prop-2-enoate (8.7 g, 34.8 mmol) were heated in a minimum of DMSO (~10 ml) under vacuum for 24 hr. The product was precipitated by the addition of water (50 ml). The solid was dried overnight in a vacuum oven and dissolved in DMSO (40 ml) containing a large excess of K<sub>2</sub>CO<sub>3</sub> and heated at 100°C for 30 min. After cooling to room temperature, brine (30 ml) was added and the precipitated product collected as a yellow solid (60% over two steps) (M+1, 474).

### Example 42

#### Preparation of 1,2-Difluoro-4-oxo-4*H*-pyrido[3,2,1-kl]-8-anthraquinone-5-carboxylic acid

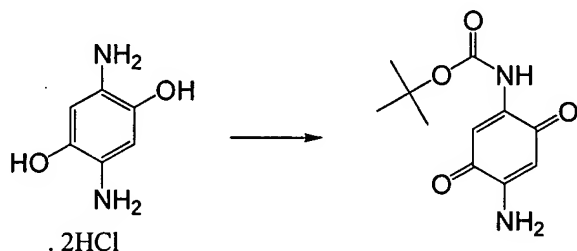


[0133] A mixture of ethyl 1,2-difluoro-4-oxo-4*H*-pyrido[3,2,1-kl]-8-anthraquinone-5-carboxylate (3.5 g, 6.8 mmol) in acetic acid:conc. HCl (1:1) (50 ml each) was heated at reflux for 2 hr. After cooling to room temperature, water (50 ml) was added and the product collected as yellow solid (94%) (M+1, 446).

### Example 43

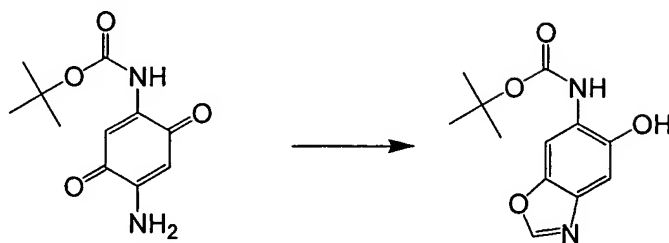
#### Preparation of Ethyl 1,2-Difluoro-4-oxo-4*H*-pyrido[3,2,1-kl]-8-phenyl-phenoxazole-5-carboxylate

#### 2-amino(t-butoxy carbonyl)-5-amino hydroquinone



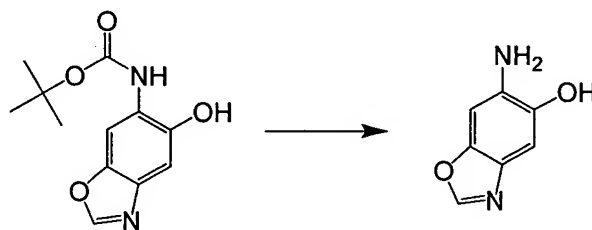
[0134] A solution of Boc anhydride (7.17 g, 33 mmol) and DIEA (17 ml, 99 mmol) in DMSO (20 ml) was added dropwise at room temperature to stirred solution of 1,4-dihydroxy-2,5-diaminobenzene (7 g, 33 mmol). After stirring for 18 hr, the product was separated between EtOAc and brine and the organic layers combined and dried over MgSO<sub>4</sub>. After removal of solvent the residue was subjected to column chromatography on silica eluting with 25-50% EtOAc in hexane to give pure product (45%) (M+1,239).

4-hydroxy-3-amino(t-butoxy carbonyl)-phenoxazole



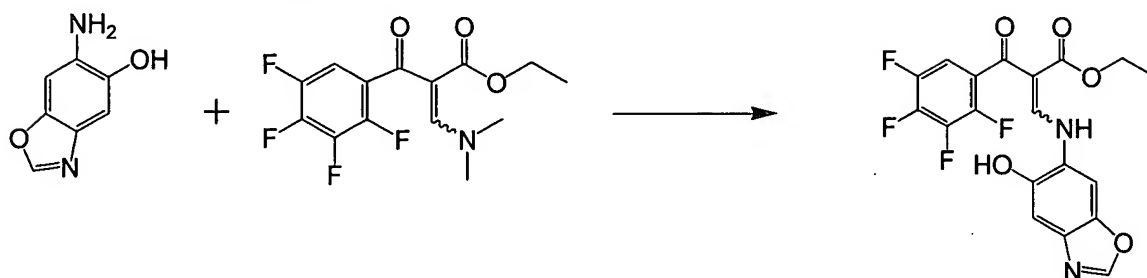
[0135] To solution of 2-amino(t-butoxy carbonyl)-5-amino hydroquinone (4.69 g, 23.3 mmol) dissolved in acetonitrile/water (1:1; 20 ml) was added Na hydrosulfite (large excess) and the mixture stirred at room temp. for 15 min. The acetonitrile was removed *in vacuo* and the aqueous mixture extracted with EtOAc (3 x 20 ml). Combined organic layers were dried over MgSO<sub>4</sub> and solvent removed *in vacuo*. The residue was taken up in neat triethyl orthoformate (100 ml), left to stir for 16 hr then heated to reflux for 10 min. The product was precipitated following cooling to room temp. by the addition of water (83%)(M+1, 251).

4-hydroxy-2-amino phenoxazole



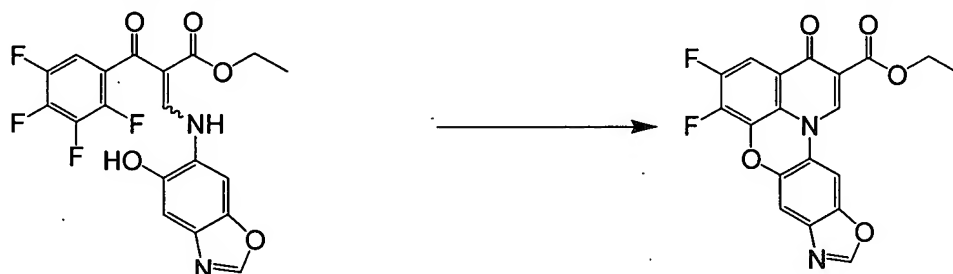
[0136] 4-Hydroxy-3-amino(t-butoxy carbonyl)-phenoxazole (3 g, 12 mmol) was dissolved in neat TFA (100 ml) and allowed to stir at room temperature for 1 hour. TFA was removed *in vacuo* to leave the final product as a TFA salt (quant.) (M-1, 149)

Ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(N-(4-hydroxy-2-amino  
phenoxazole))-prop-2-enoate



[0137] A solution of ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(dimethylamino)-prop-2-enoate (7.34 g, 23 mmol) and 2-amino-4-phenyl-phenol (3.45 g, 23 mmol) in EtOAc (20 ml) containing triethylamine (10 ml) was stirred under vacuum on the rotary evaporator for 3 hours. The EtOAc was removed *in vacuo* and the residue subjected to column chromatography on silica eluting with 50% EtOAc in hexane to give pure product (72%) (M+1, 425).

Ethyl 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-phenyl-phenoxazole-5-carboxylate

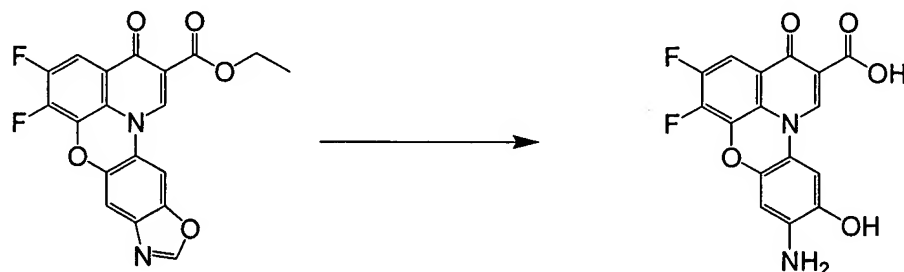


[0138] A solution of ethyl-2-(2',3',4',5'-tetrafluorobenzoyl)-3-(N-(4-hydroxy-2-amino phenoxazole))-prop-2-enoate (3.5 g, 8.25 mmol) in DMSO (50 m) containing K<sub>2</sub>CO<sub>3</sub> (large excess) was heated at 80°C for 10 min. After cooling to room temperature, water was added to precipitate the product as a yellow sold (82%) (M+1, 385).

Example 44

Preparation of

1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-(3'-hydroxy-4'-amino phenyl)-5-carboxylic acid

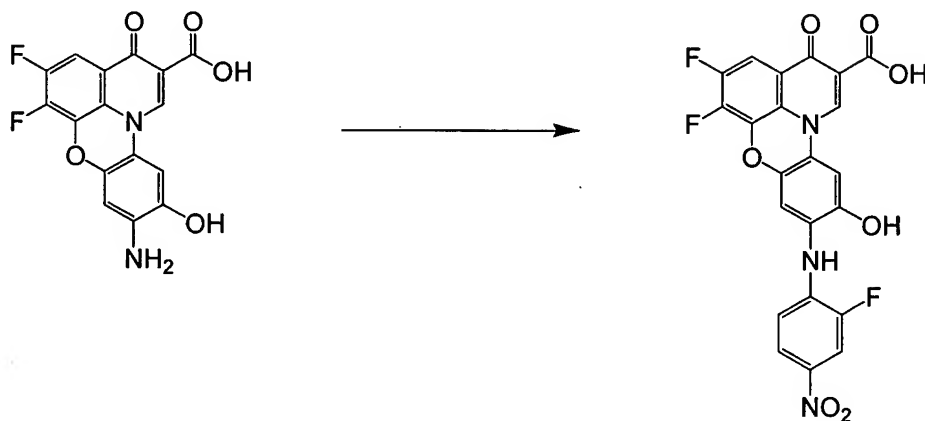


[0139] A mixture of ethyl 1,2-difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-phenyl-phenoxazole-5-carboxylate (2.3 g, 6 mmol) in acetic acid:conc. HCl (1:1; 100 ml) was heated to reflux for 30 min. After cooling to room temp., volatiles were removed *in vacuo* to leave the product as a brown solid (82%) (M+1, 347).

Example 45

Preparation of 1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-(nitro-phenoxazine)-5-carboxylic acid

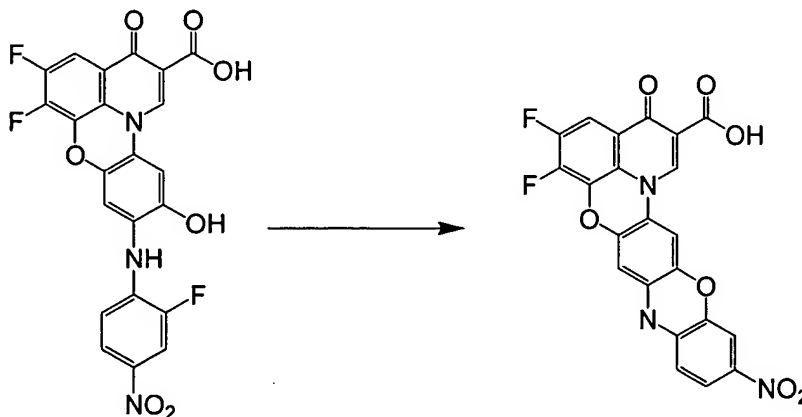
1,2-Difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-(3'-hydroxy-4'-amino-  
(N-2''-fluoro-4''-nitro phenyl)-phenyl))-5-carboxylic acid



[0140] A solution of 1,2-difluoro-4-oxo-4H-pyrido[3,2,1-kl]-8-(3'-hydroxy-4'-amino phenyl)-5-carboxylic acid (0.5 g, 1.44 mmol), 3,4-difluoro-nitro benzene (0.5 ml, 4.3 mmol) and

DIEA (1 ml) was heated to 90°C in NMP (50 ml) for 30 min. After cooling to room temp. the product was precipitated by the addition of water and filtered (63%) (M+1, 486).

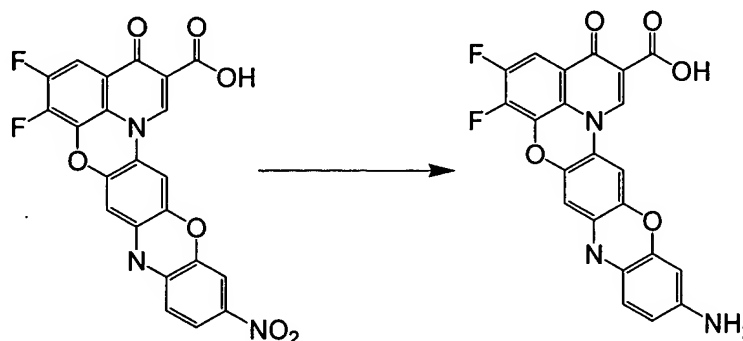
1,2-Difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]-8-(nitro-phenoxazine)-5-carboxylic acid



[0141] A solution of 2-difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]-8-(3'-hydroxy-4'-amino phenyl)-5-carboxylic acid (0.3 g, 0.6 mmol) in DMSO (50 ml) containing an excess of K<sub>2</sub>CO<sub>3</sub> was stirred and heated to 110°C for 1 hr. After cooling to room temp. the product was precipitated by the addition of 3M HCl and filtered (71%) (M+1, 465).

Example 46

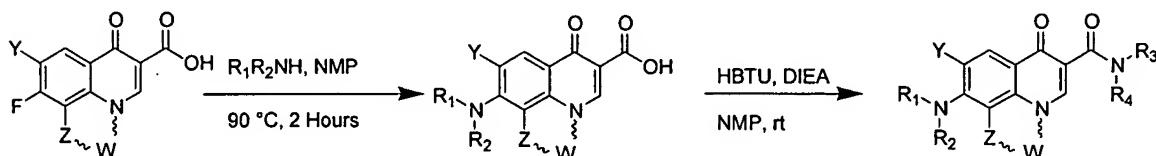
Preparation of 1,2-Difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]-8-(amino-phenoxazine)-5-carboxylic acid



[0142] A mixture of 1,2-difluoro-4-oxo-4*H*-pyrido[3,2,1-*kl*]-8-(nitro-phenoxazine)-5-carboxylic acid (0.1 g, 0.2 mmol) and Tin (II) chloride (0.15 g, 0.6 mmol) in acetic acid:conc. HCl (1:1; 50 ml) was heated to reflux for four hr. After cooling to room temp. the product was precipitated by the addition of water and filtered (72%) (M+1,435).

### Example 47

#### Preparation of Preparation of amide derivatives of substituted quinobenzoxazine analogs



[0143] To a series of solutions of the fluoroacid (0.5 mmol) in NMP (3.6 mL) was added the amines  $\text{NHR}_1\text{R}_2$  (0.5-2.0 mmol) at room temperature. The vessels were sealed and heated on a 90°C hotplate with constant stirring for 1-2 hours until the reactions were determined to be complete by HPLC/MS analysis. The reaction mixtures were allowed to cool to room temperature and water was added (20 mL). The resulting precipitates were collected by vacuum filtration and dried under vacuum. In cases where 1.0 equivalent of amine was used, the resulting reaction mixtures were used in the next step “as is.” The resulting solids or solutions were treated with HBTU (2.5 eq.) and DIEA in 3.6 mL NMP and allowed to stir for 30 minutes at room temperature under an inert atmosphere. These solutions were added to a series of amines  $\text{NHR}_3\text{R}_4$  (2.5 equivalents) in a 96 well format (Whatman Uniplate, 2 mL) and allowed to react for 2 hours. Methanol was then added (50-100  $\mu\text{L}$ ) and the plate was filtered (Whatman Unifilter Polypropylene). The resulting liquids were directly chromatographed on reverse HPLC (Waters Xterra 19X50 mm) with mass directed collection (Micromass ZQ, Waters FCII). The fractions were analyzed for purity (MS TIC, UV) and dried by vacuum evaporation (Savant) with an average yield of 5-10 mg). Tables 1 and 2 list exemplary ester-substituted and amide-substituted quinobenzoxazines analogs, respectively.

### Example 48

#### Antitumor Data

[0144] Two xenograft models for inoculation were harvested and diluted to a concentration of  $50 \times 10^6$  cells/ml or  $100 \times 10^6$  cells/ml. Four to six week old nude mice were injected with 0.1 ml of the cell suspension which contains between  $5 \times 10^6$  and  $10 \times 10^6$  cells. When tumors are of a suitable size compound dosing is commenced. Tumor sizes are measured throughout the treatment period with calipers and body weights also measured.

[0145] Antitumor activities for compounds CX-3092 (1204) and CX-1535 (148) are shown in Figures 1 and 2, indicating efficacy (slow tumor weight gain) and a lack of toxicity (little body weight change). Figure 1 shows the antitumor activity of compound **494** in Ramos, a model for fatal childhood leukemia. Figure 2 shows the antitumor activity of compound **516** in HCT-116, a model of colorectal cancer.

#### Example 49

##### Cell Proliferation and/or Cytotoxicity Assay

###### Cell Culture

[0146] Human cervical epithelial cells (HeLa cells) were obtained from American Type Culture Collection (Manassas, VA). Cells were grown in Eagle's minimum essential medium (MEM, Hyclone, Utah) supplemented with 2 mM Glutamine, 0.1 mM nonessential amino acid, 1 mM Na Pyruvate, 1.5 g/L NaHCO<sub>3</sub>, 50 mg/L gentamicin, and 10% fetal bovine serum (Hyclone, USA) in a humidified atmosphere of 5% CO<sub>2</sub> at 37°C.

###### MTS Assay

[0147] Antiproliferative effects of anticancer drugs were tested by the CellTiter 96 AQueous assay (Promega, WI), which is a colorimetric assay for determining the number of viable cells. (See, e.g., Wang, L., *et al.*, *Methods Cell Sci* (1996) 18:249-255).

[0148] Cells (4,500 cells/well) were seeded on 96 well flat bottom plates (Corning, NY) in 100 µl of culture medium without any anticancer drug on day 0, and the culture medium was exchanged for that contained anticancer drugs at various concentrations on day 1. After incubation for 3 days under normal growth conditions (on day 4), the monolayers were washed once in PBS, and the medium was switched to 100 µl of PBS in each of the 96 well plate. After mixing MTS and PMS at the ratio of 20:1, 20 µl of MTS/PMS solution was added to each of the 96 well plate and incubated for 4 hours in a humidified atmosphere of 5% CO<sub>2</sub> at 37°C. The absorbance was read at 490 nm using FLUOstar Galaxy 96 well plate reader (BMG Labtechnologies, Germany). µM concentrations (MTS data) reported in Tables 1-2 are concentrations at which 50 % of



antiproliferative cell response is seen. Compounds whose  $IC_{50}$  values were greater than 5  $\mu$ M were not reported.

### Example 50

#### Measurement of mRNA values in Cell Assays

[0149] Real-time quantitative PCR (QPCR) method was used to detect accurately the changes of the target c-myc and the endogenous reference GAPDH gene copies in the same tube. Cells (15,000 cells/well) were seed on 96 well flat bottom plates (Corning, NY) and incubated under normal growth conditions for overnight. The next day, the culture medium was exchanged for that contained anticancer drugs at various concentrations and incubate for 4 hrs in a humidified atmosphere of 5%  $CO_2$  at 37°C. Total RNA (tRNA) was extracted using the RNeasy 96 Kit (QIAGEN, CA). The concentration of the tRNA was determined by the RiboGreen RNA Quantitation Reagent (Molecular Probes, OR).

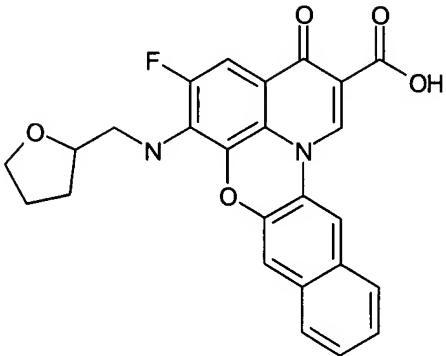
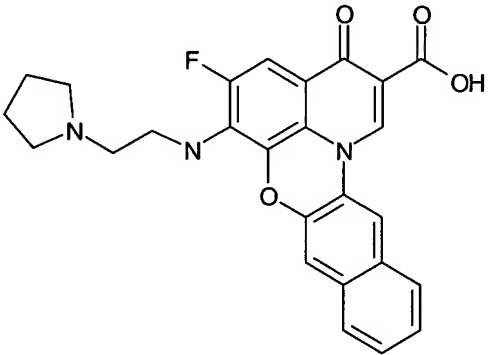
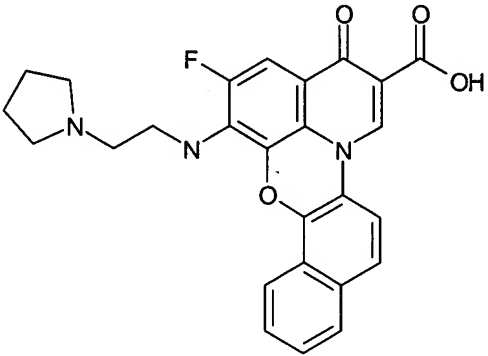
[0150] Reverse-transcription (RT) reaction was occurred using 50 ng of tRNA from each well in a 25  $\mu$ l reaction containing 1x TaqMan RT buffer, 2.5 uM random hexamers, 5.5 mM  $MgCl_2$ , 0.5 mM each deoxynucleoside triphosphate (dNTP), 30 U MultiScribe Reverse Transcriptase, and 10 U RNase inhibitor. RT reactions were incubated for 10 min at 25°C, reverse-transcribed for 30 min at 48°C, inactivated for 5 min at 95°C, and placed at 4°C. All RT reagents were purchased from Applied Biosystems, CA.

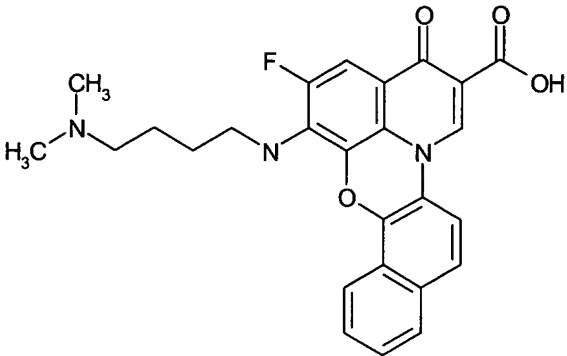
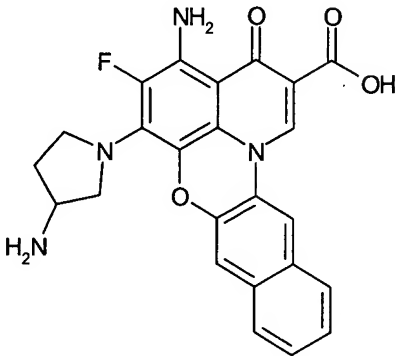
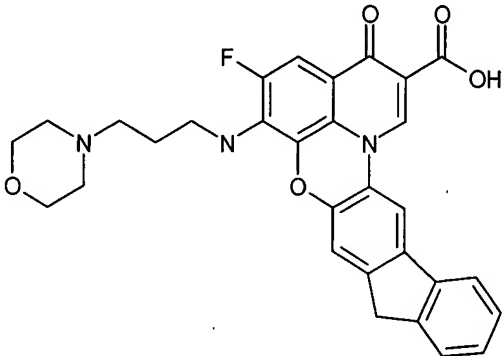
[0151] Real-Time QPCR reaction was performed in a 50  $\mu$ l reaction containing the 5  $\mu$ l of cDNA, 1x Universal PCR Master Mix, 1x c-myc Pre-Developed Primers and Probe set, and 0.8 x GAPDH Pre-Developed Primers and Probe set. Because of the relative abundance of GAPDH gene in Hela, GAPDH primers and probe concentration were adjusted to get accurate threshold cycles ( $C_T$ ) for both genes in the same tube. The threshold cycle ( $C_T$ ) indicates the fractional cycle number at which the amount of amplified target reaches a fixed threshold. By doing so, the GAPDH amplification was stopped before it can limit the common reactants available for amplification of the c-myc, resulted in a reduction in  $\Delta Rn$  value of GAPDH, but no effect on its  $C_T$  value, and equal amplification efficiency for both genes. The  $\Delta Rn$  value represents the normalized reporter signal minus the baseline signal.  $\Delta Rn$  increases during PCR as amplicon copy number increases until the reaction approaches a plateau.

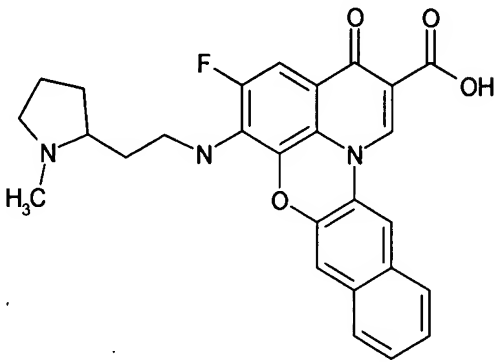
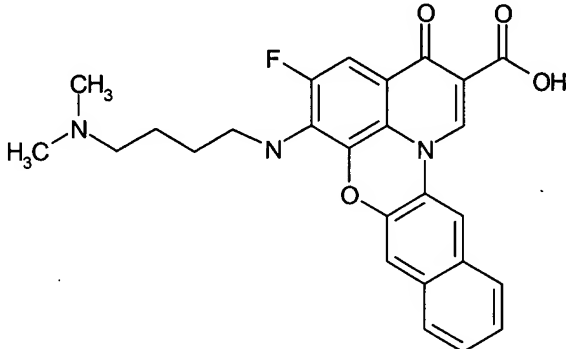
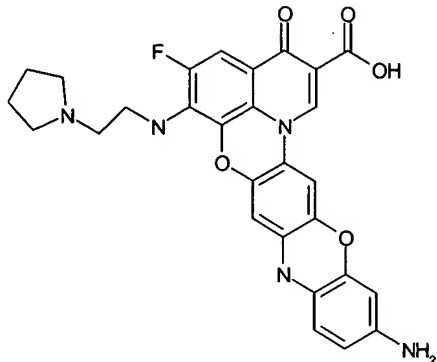
[0152] The c-myc probe was labeled with 6FAM™ dye-MGB and the GAPDH probe was labeled with VIC™ dye-MGB. Preincubation was performed for 2 min at 50°C to activate AmpErase UNG enzyme and then for 10 min at 95°C to activate AmpliTaq DNA Polymerase. DNA was amplified for 40 cycles of 15 sec at 95°C and 1 min at 60°C. Human c-myc and GAPDH cDNA were amplified, detected, and quantitated in real time using the ABI Prism 7000 Sequence Detection system (Applied Biosystems, CA), which was set to detect both 6-FAM and VIC reporter dyes simultaneously.

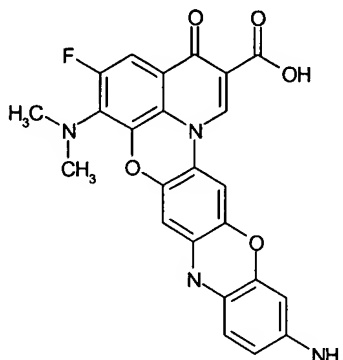
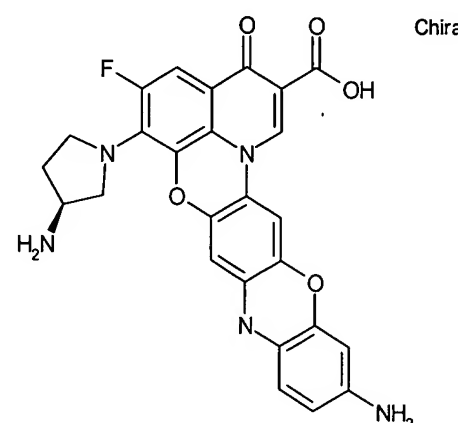
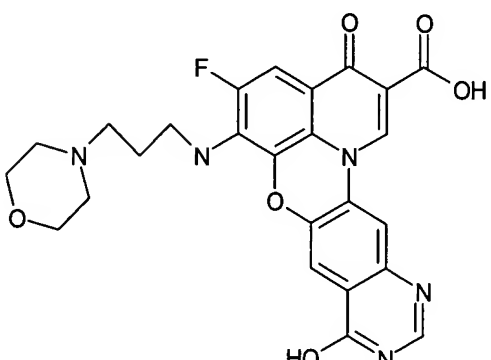
[0153] The data was analyzed by using the ABI PRISM Sequence Detection System and Microsoft Excel. Relative quantitation was done using the standard curve and comparative C<sub>T</sub> method at the same time, and both methods gave equivalent results. The cycle at which the amplification plot crosses the C<sub>T</sub> is known to accurately reflect relative mRNA values. (See, Heid, *et al.*, *Genome Res.* (1996) 6:986-994; Gibson, *et al.*, *Genome Res.* (1996) 6:995-1001). QPCR reactions were set up in triplicate at each cDNA sample and the triplicate C<sub>T</sub> values were averaged. All reagents including Pre-Developed Primers and probe set were purchased from Applied Biosystems, CA.  $\mu$ M concentrations (STOP data) reported in Tables 1-2 are concentrations at which 50 % inhibition of c-myc mRNA levels are seen. Compounds whose IC<sub>50</sub> values were greater than 5  $\mu$ M were not reported.

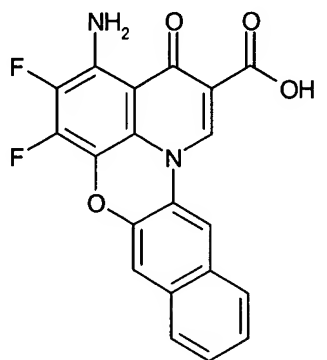
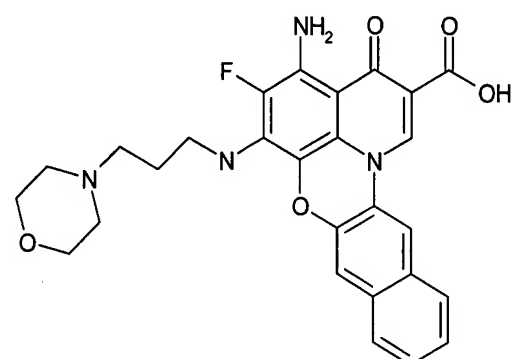
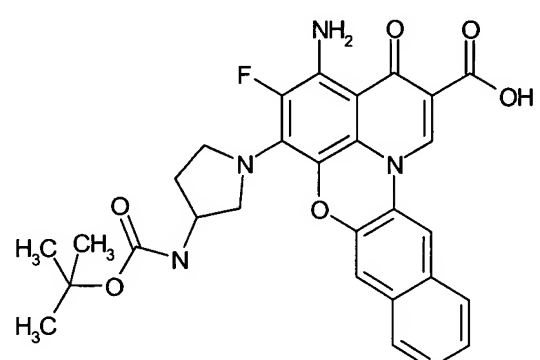
[0154] It is understood that the foregoing detailed description and accompanying examples are merely illustrative, and are not to be taken as limitations upon the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use of the invention, may be made without departing from the spirit and scope thereof. U.S. patents and publications referenced herein are incorporated by reference.

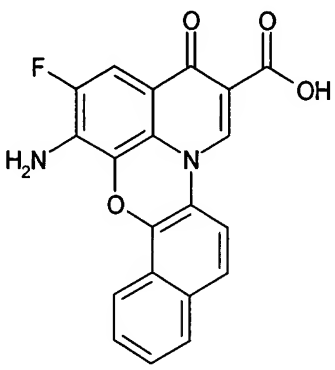
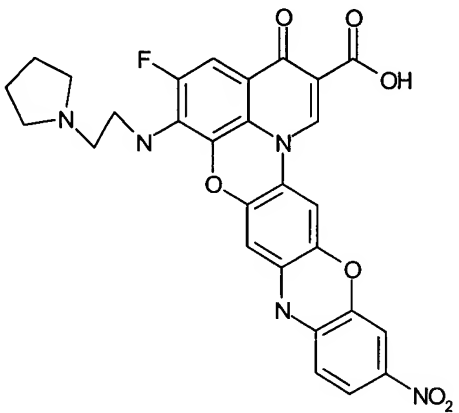
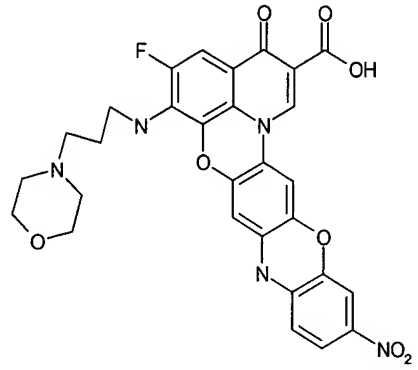
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
<b><u>Table 1</u></b>			
1		4	
2		2.5	
3		2.5	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
4		1.76	
5		1.75	7.20
6		1.75	

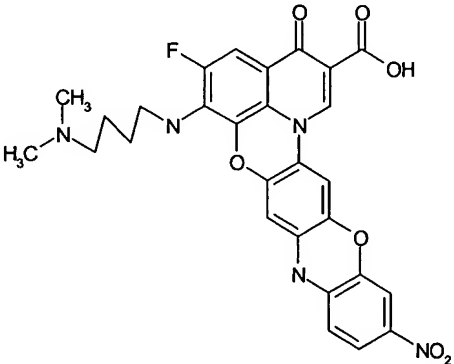
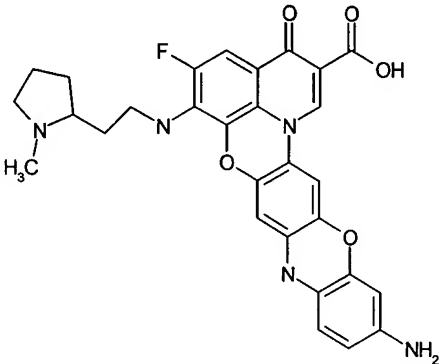
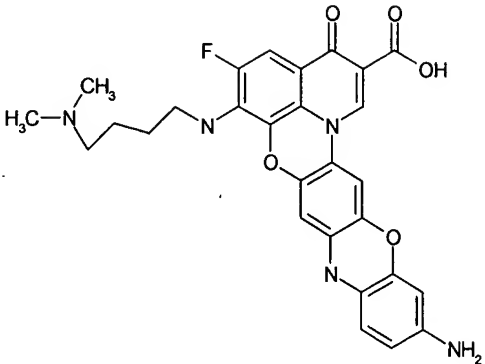
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7		1.75	
8		1.75	
9		1.75	

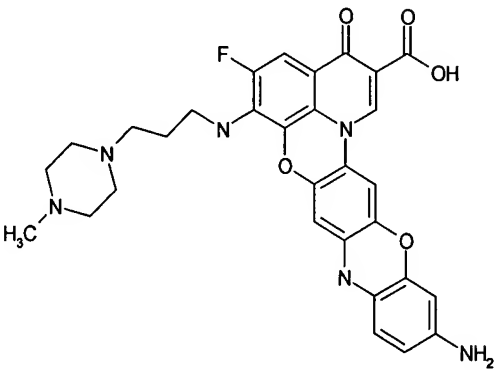
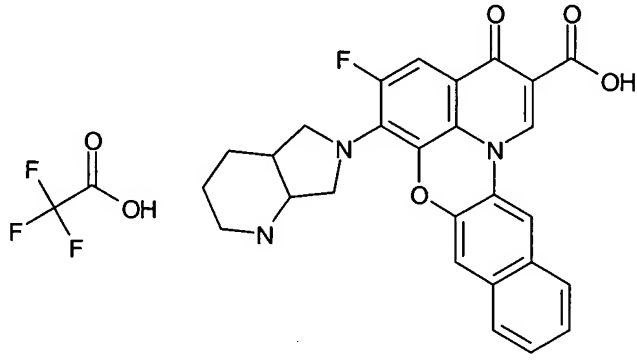
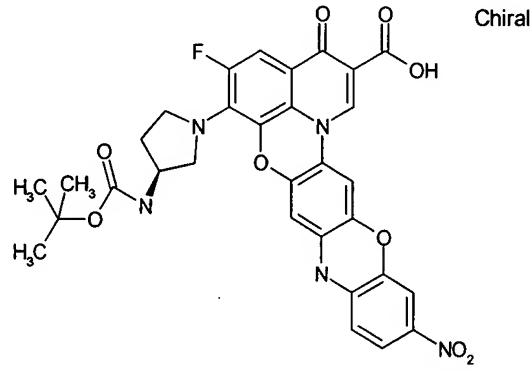
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10		1.75	
11		1.75	
12		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
13		1.75	
14		1.75	
15		1.75	

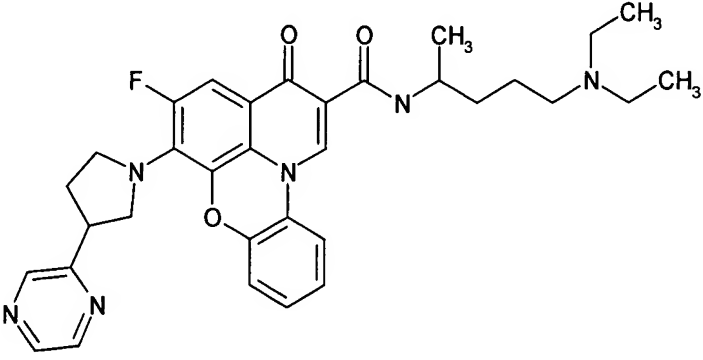
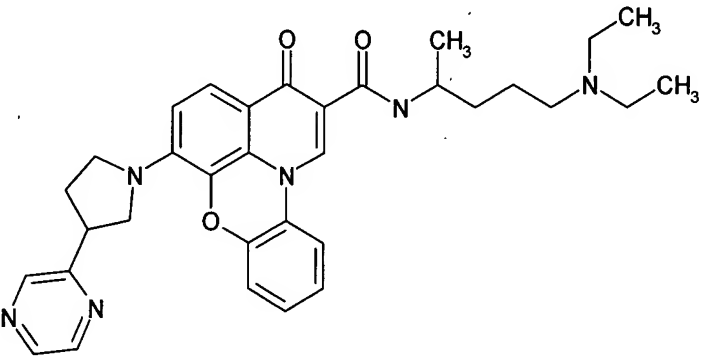
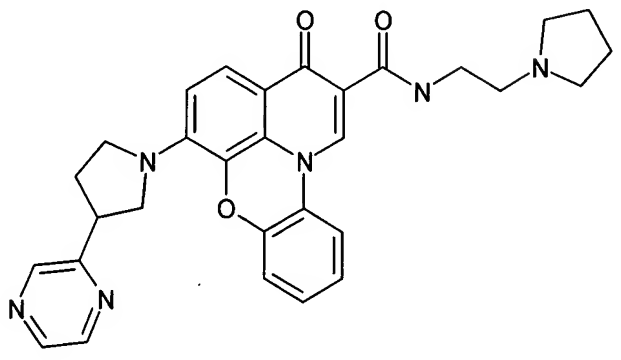
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16		0.9	
17		0.75	
18		0.75	

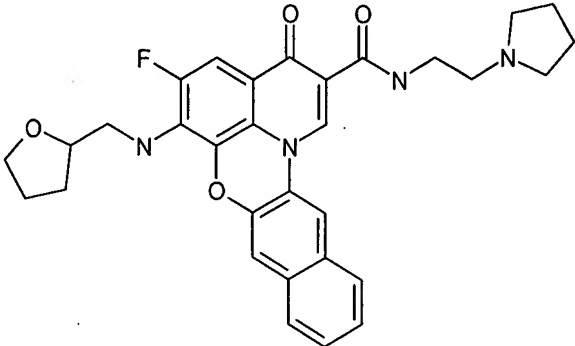
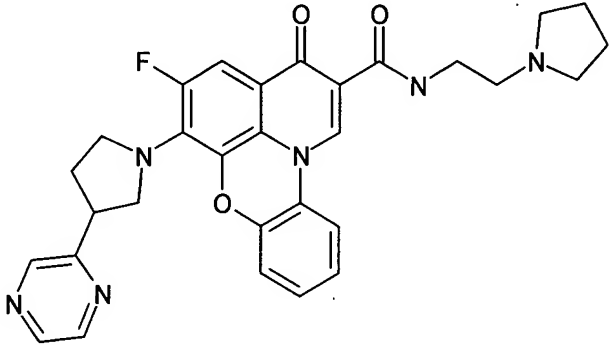
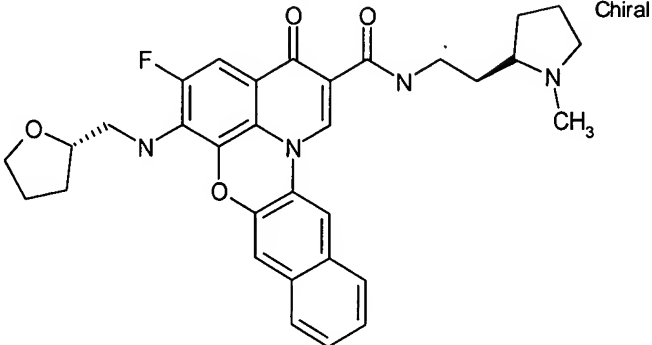


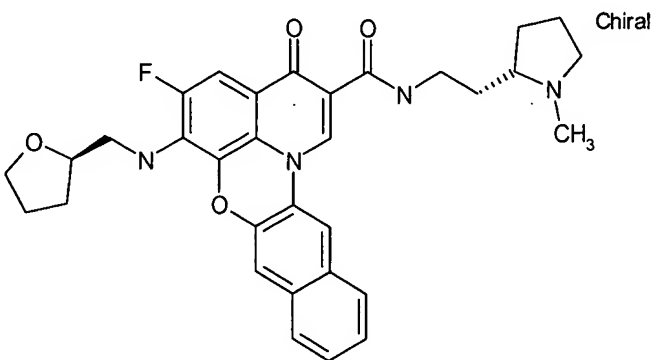
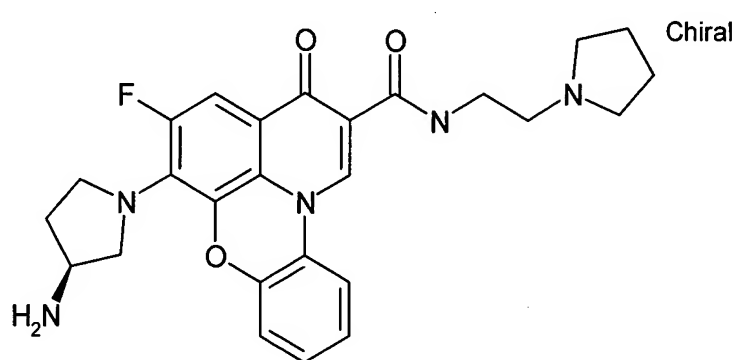
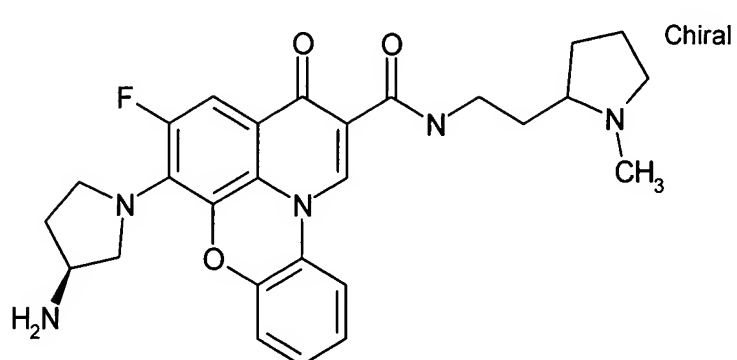
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19		0.75	
20		0.75	
21		0.75	

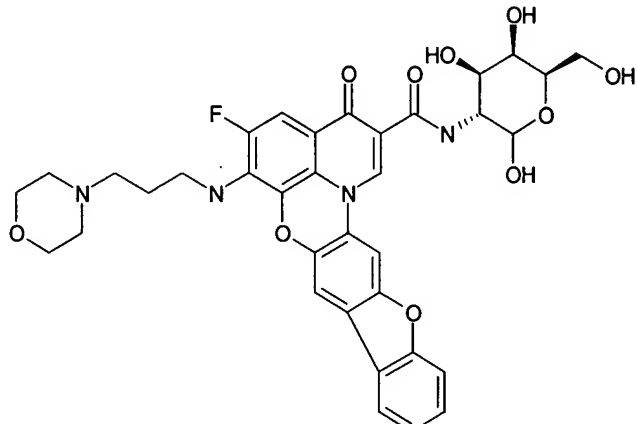
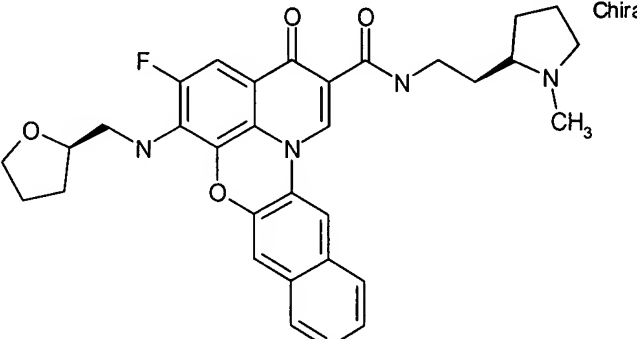
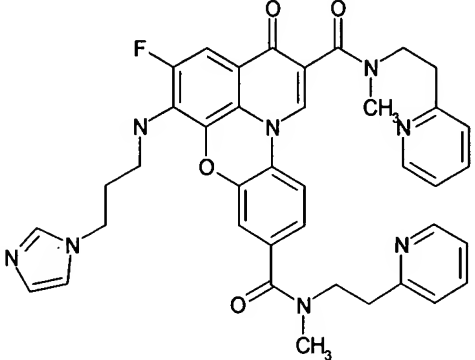
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
22		0.75	
23		0.75	
24	 <p>Chiral</p>	0.5	7.00

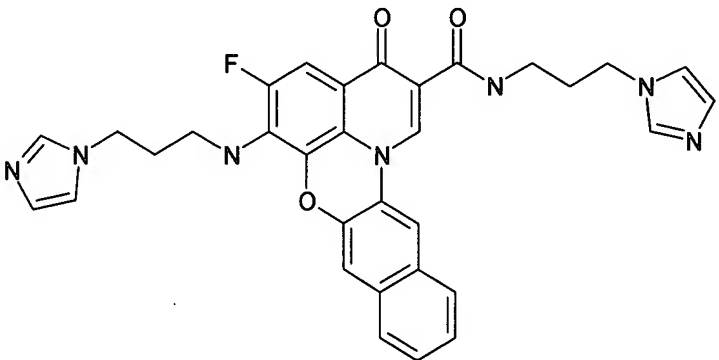
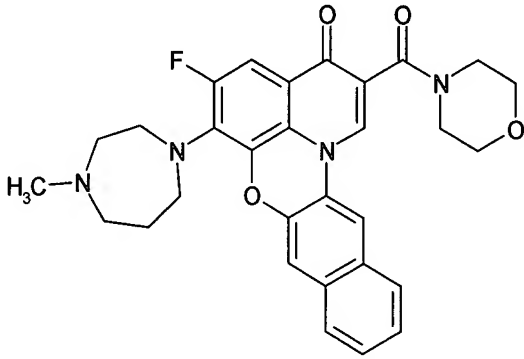
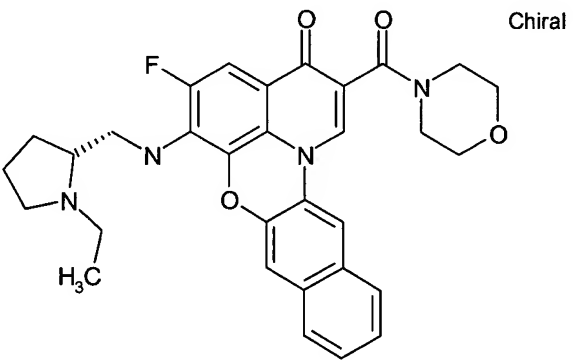
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25		0.25	0.20
<b><u>Table 2</u></b>			
26		4	0.73
27		3	3.80

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
28		3	2.50
29		3	2.00
30		3	1.80

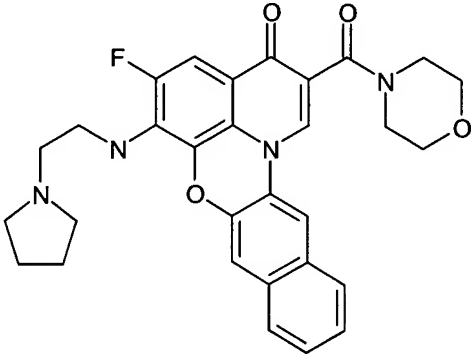
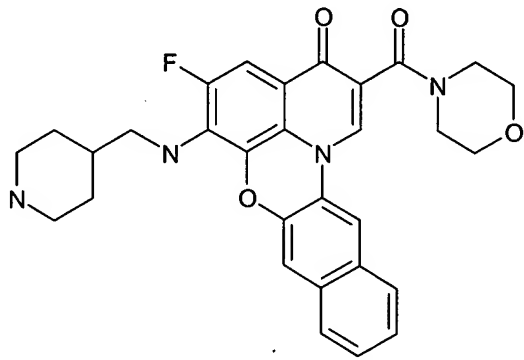
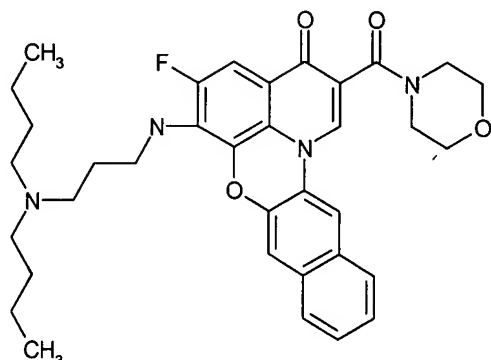
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31		3	1.40
32		3	0.60
33		3	0.29

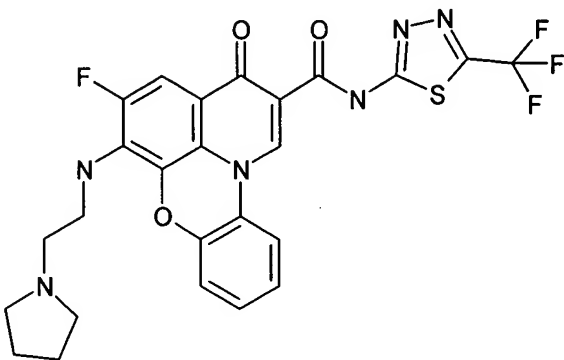
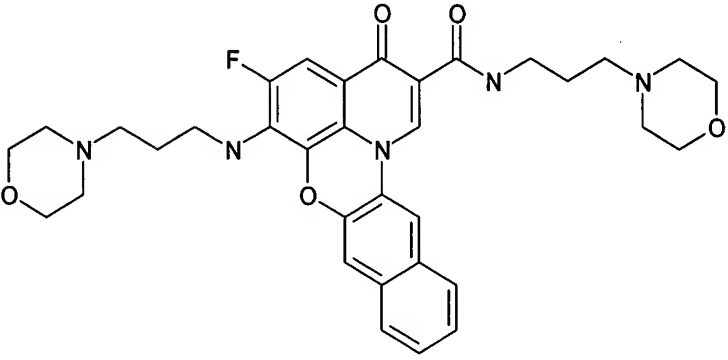
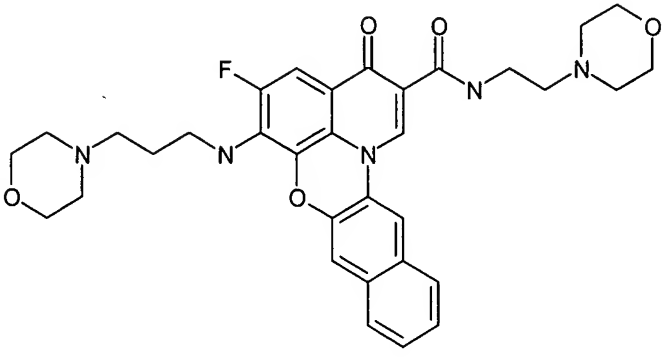
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34		3	0.28
35		3	0.21
36		3	0.16

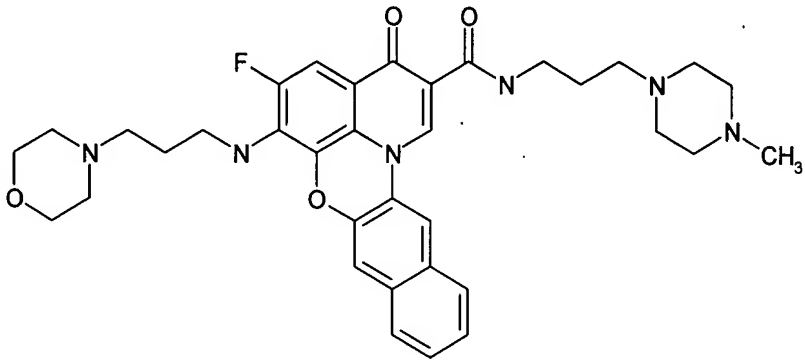
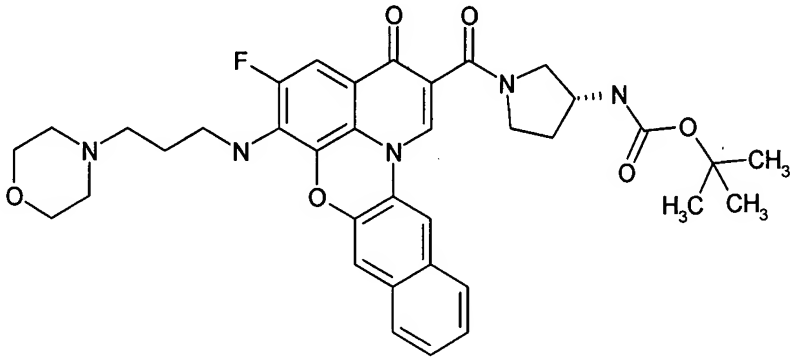
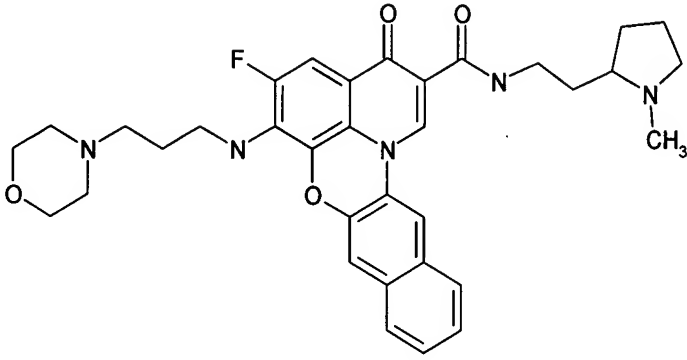
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37		2.5	2.80
38		2.5	0.26
39		2.5	

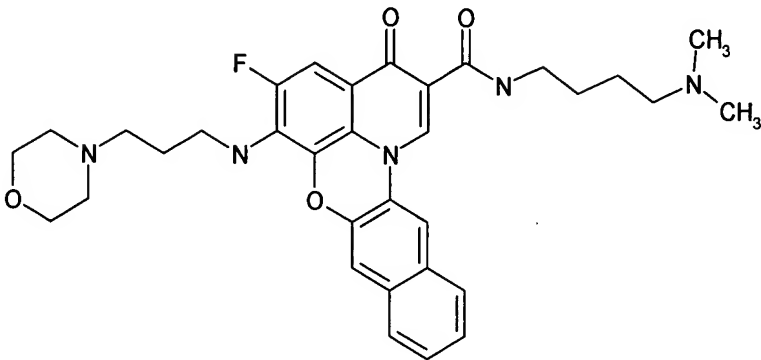
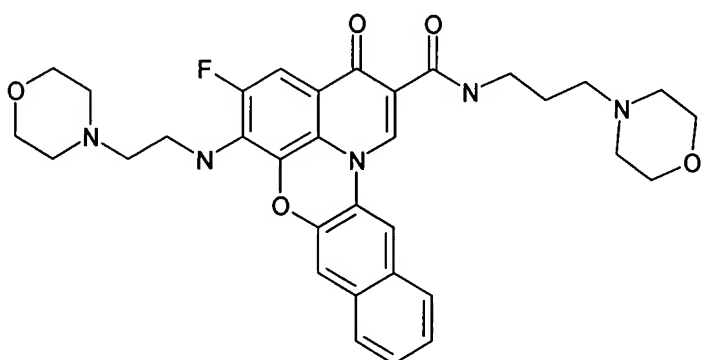
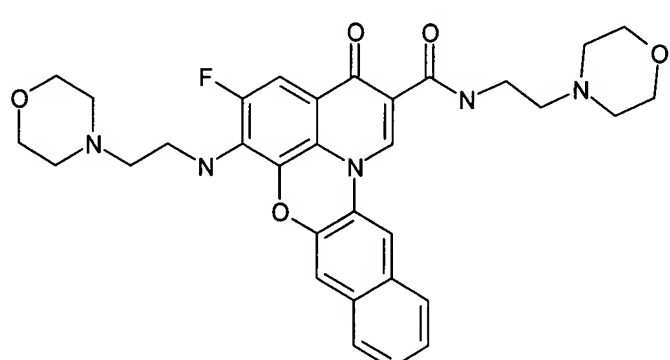
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40		2.5	
41		2.5	
42		2.5	

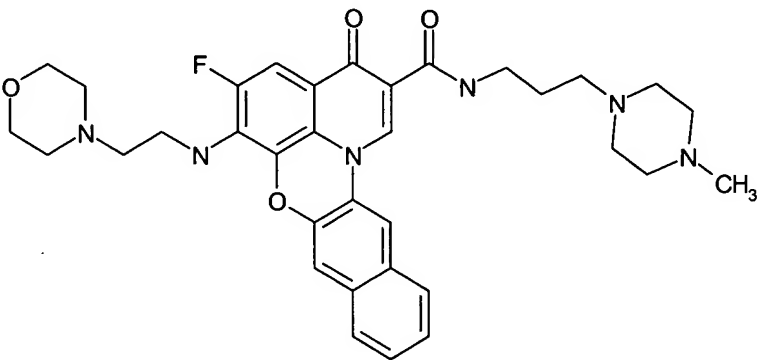
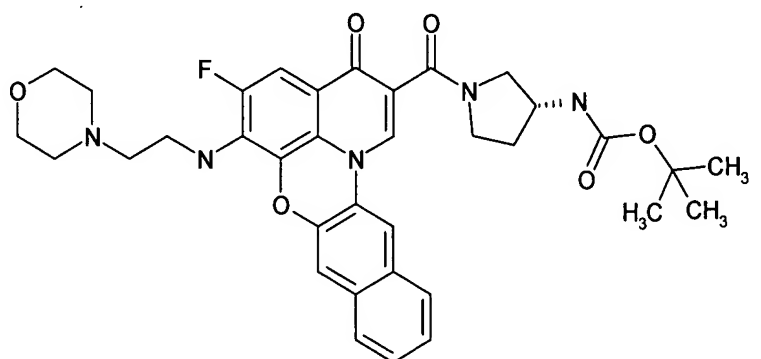
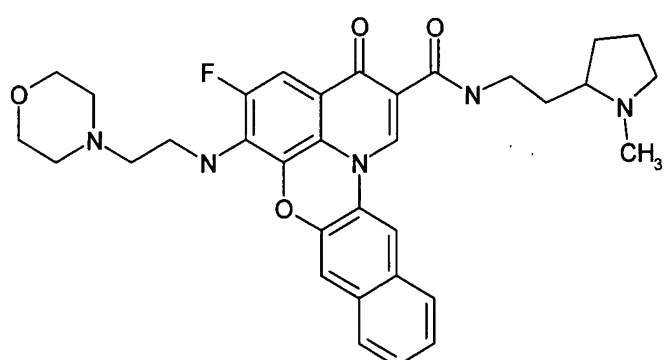


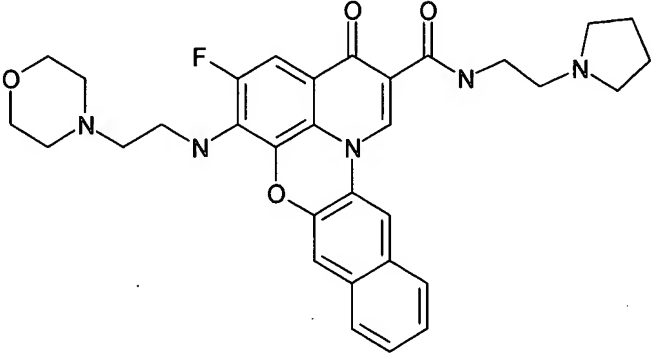
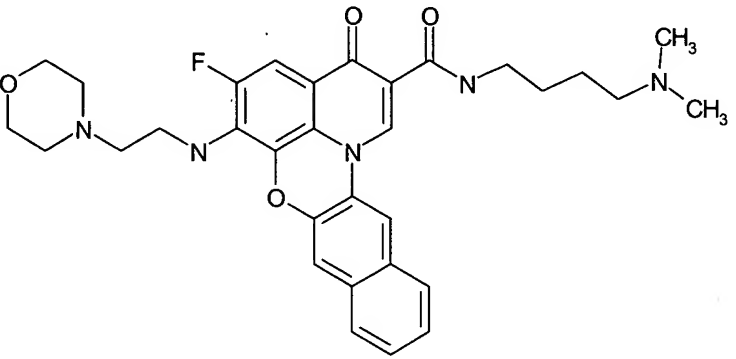
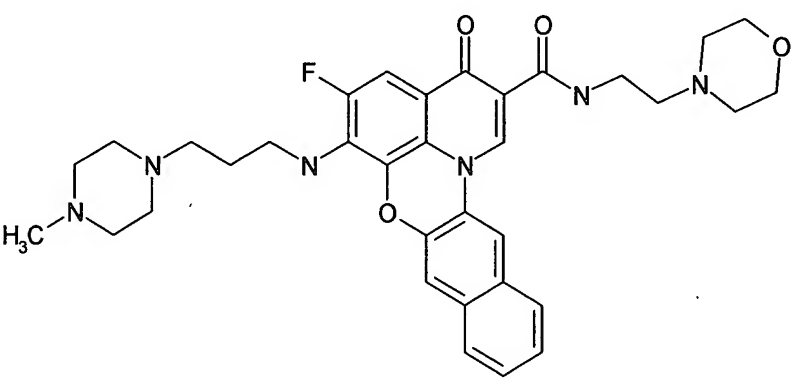
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
43		2.5	
44		2.5	
45		2.5	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
46		2.5	
47		2.5	
48		2.5	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
49		2.5	
50		2.5	
51		2.5	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
52		2.5	
53		2.5	
54		2.5	

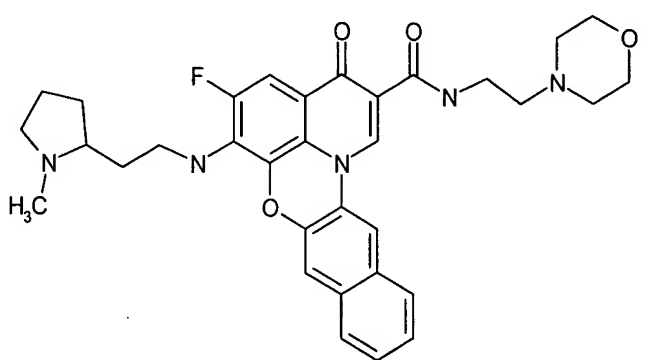
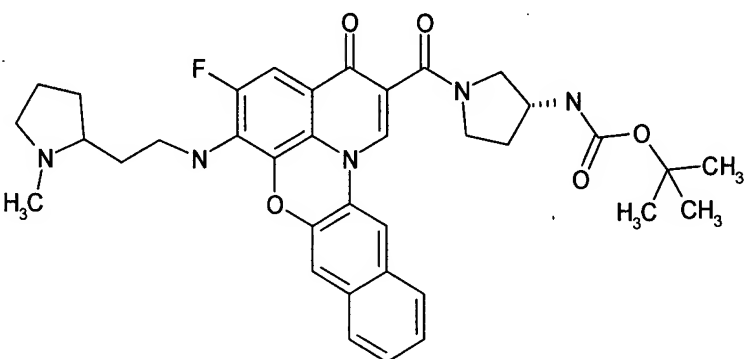
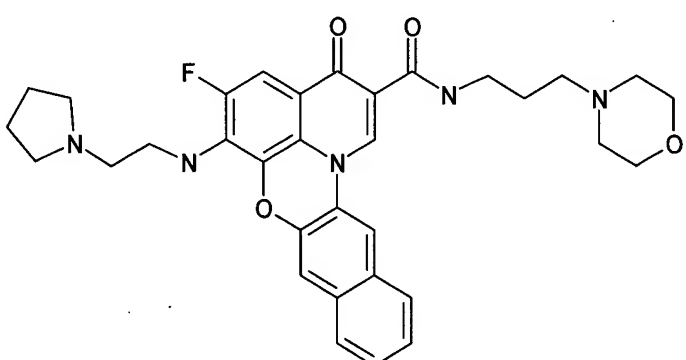
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
55		2.5	
56		2.5	
57		2.5	

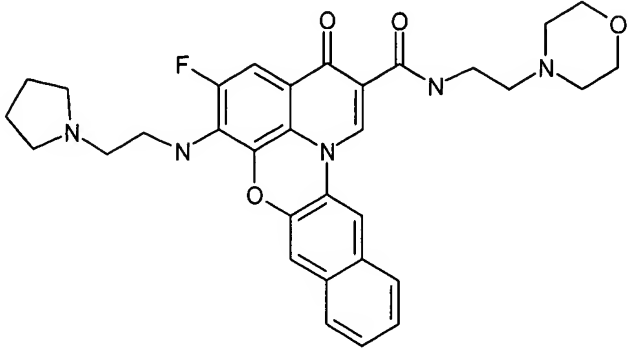
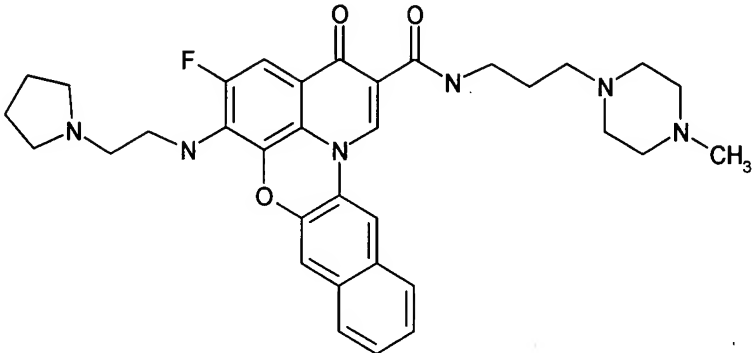
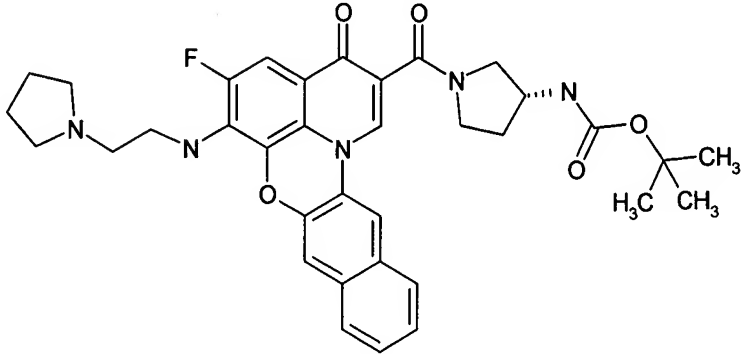
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
58		2.5	
59		2.5	
60		2.5	

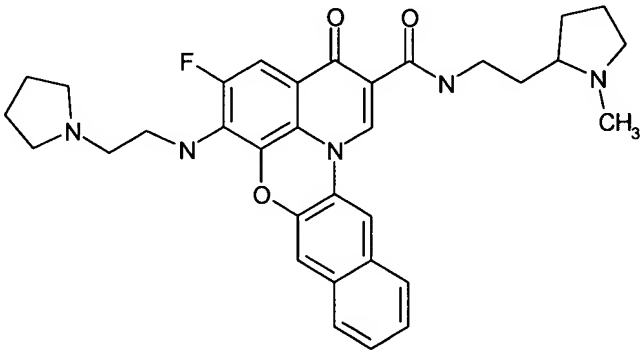
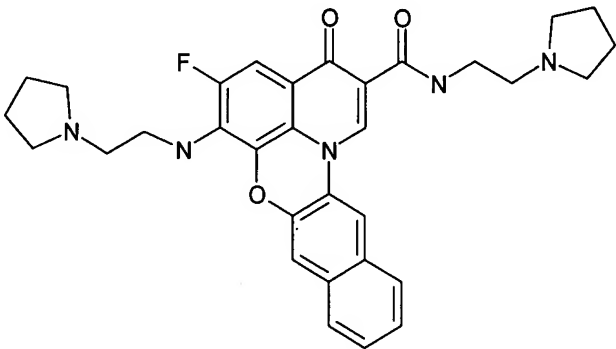
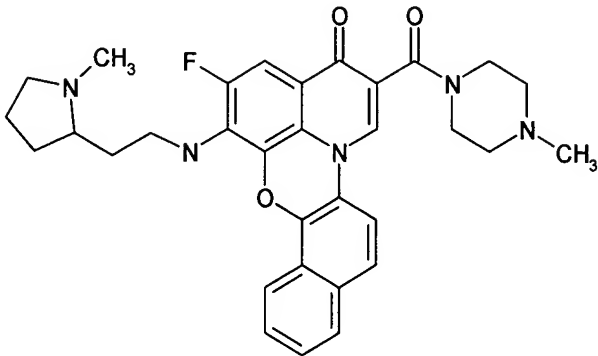
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
61		2.5	
62		2.5	
63		2.5	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
64		2.5	
65		2.5	
66		2.5	

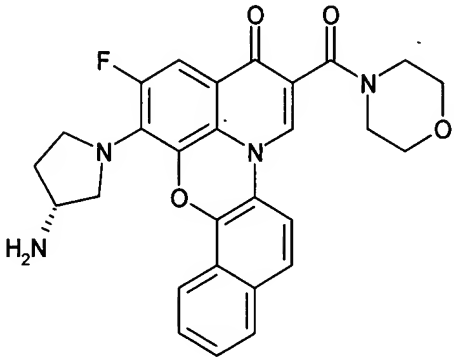
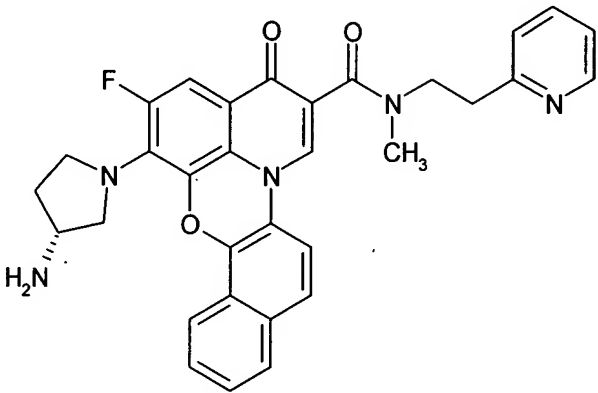
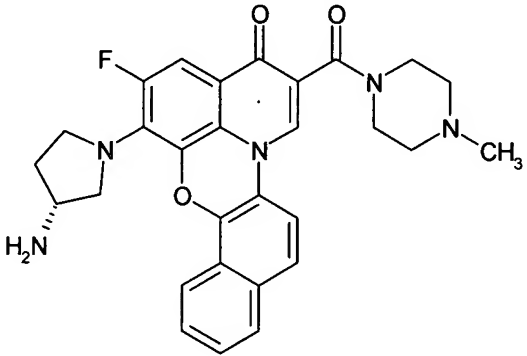


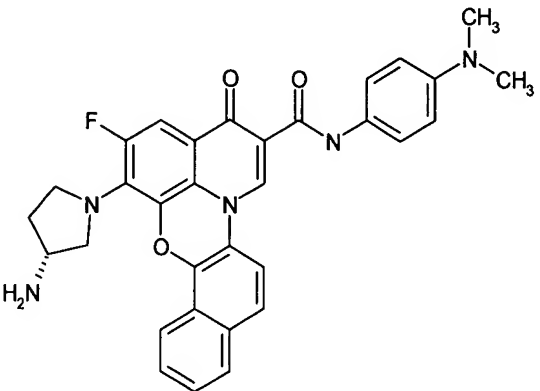
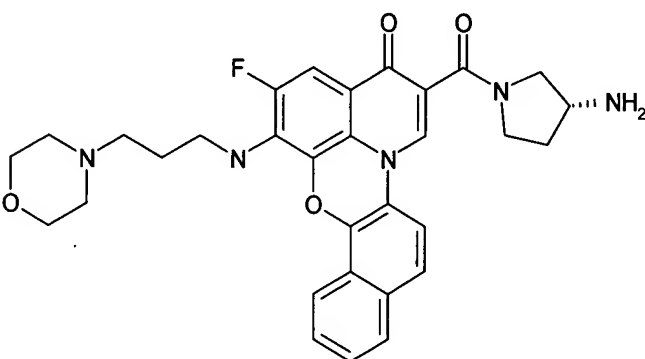
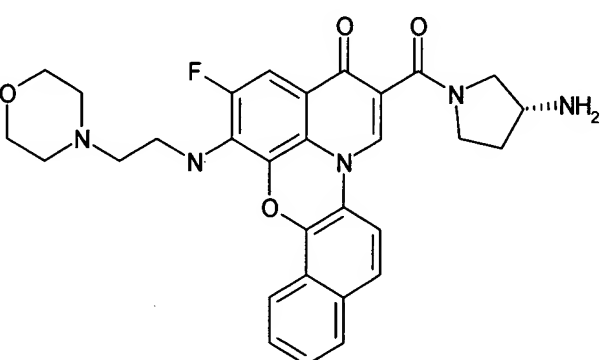
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
67		2.5	
68		2.5	
69		2.5	

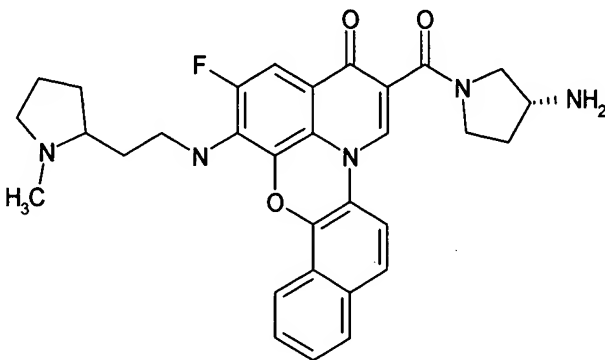
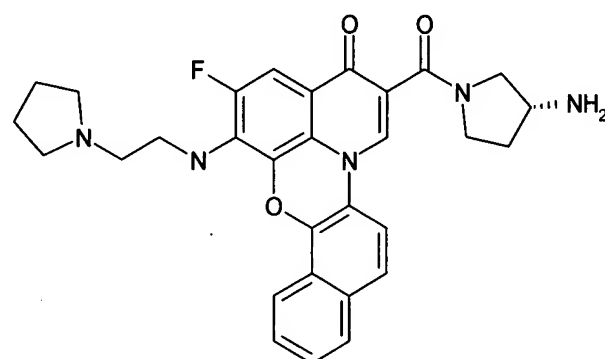
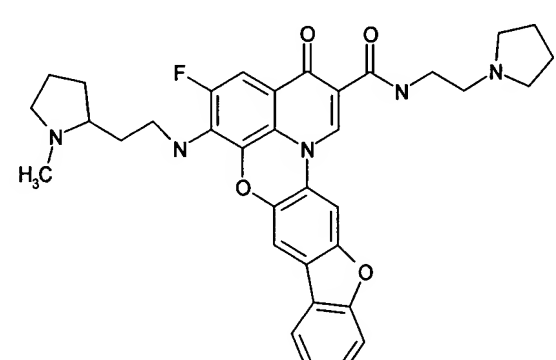
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
70		2.5	
71		2.5	
72		2.5	

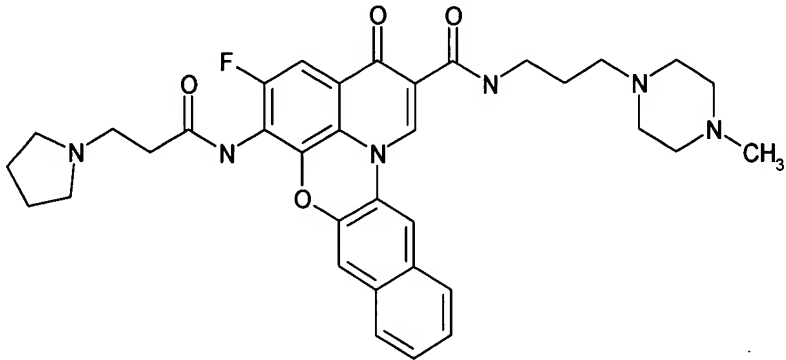
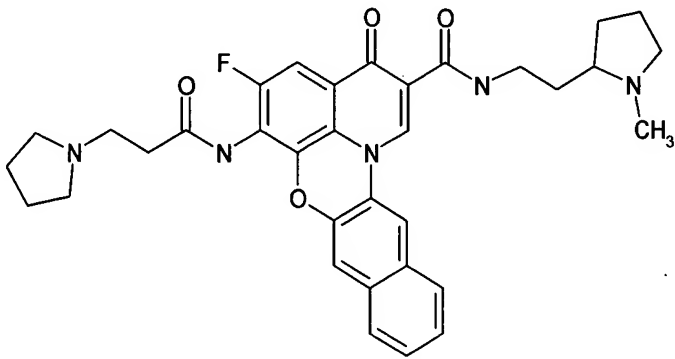
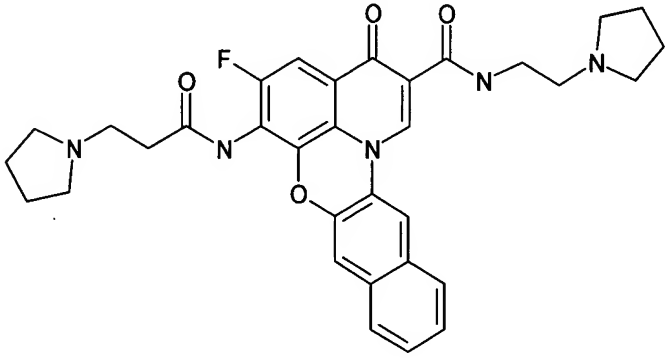
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
73		2.5	
74		2.5	
75		2.5	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
76		2.5	
77		2.5	
78		2.5	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
79		2.5	
80		2.5	
81		2.5	

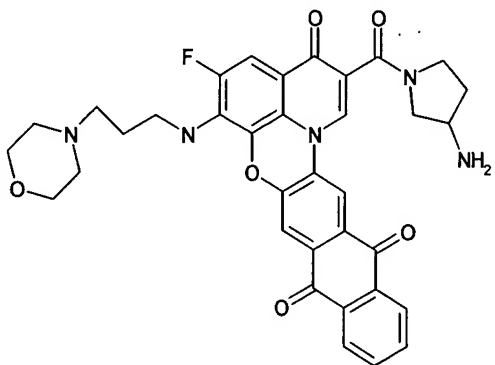
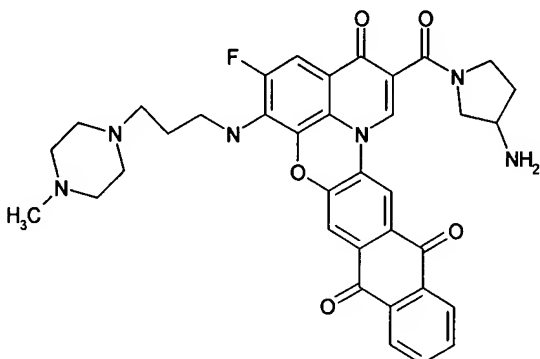
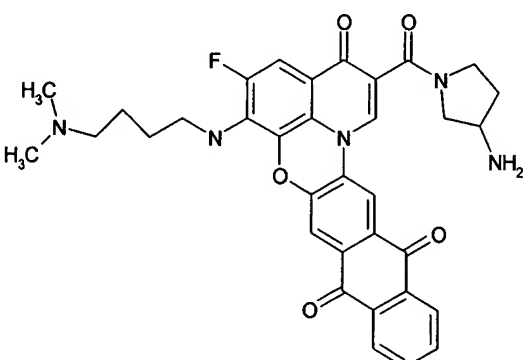
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
82		2.5	
83		2.5	
84		2.5	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
85		2.5	
86		2.5	
87		2.5	

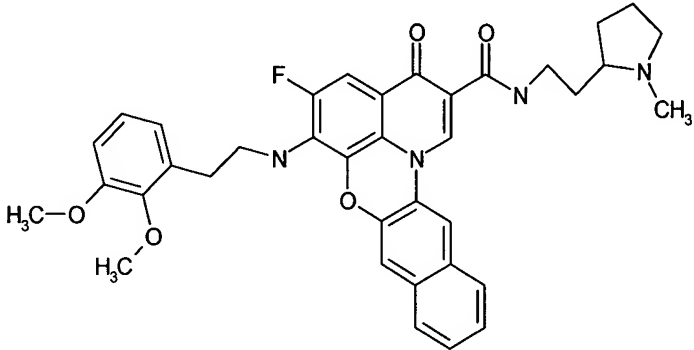
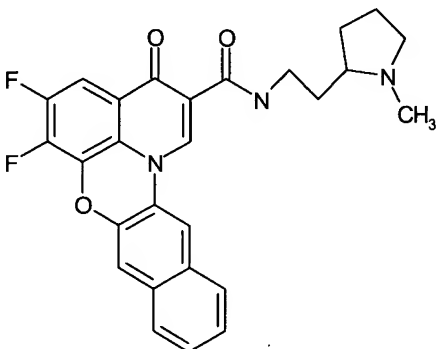
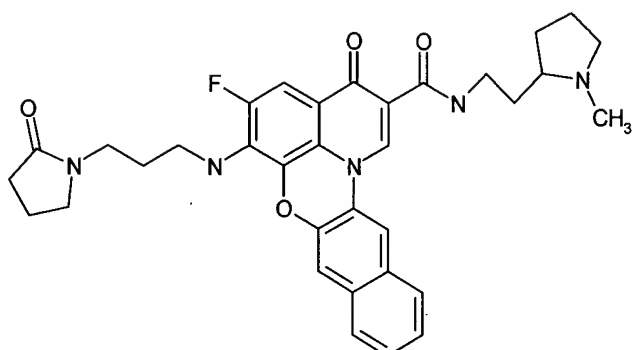
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
88		2.5	
89		2.5	
90		2.5	

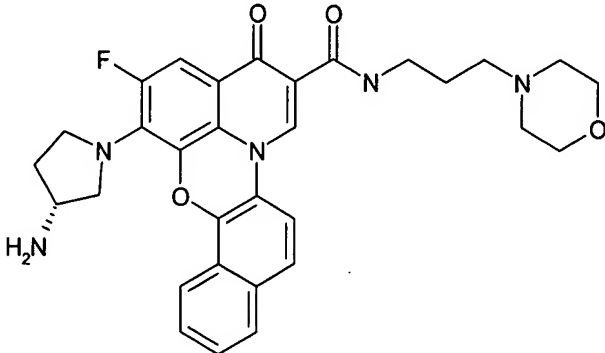
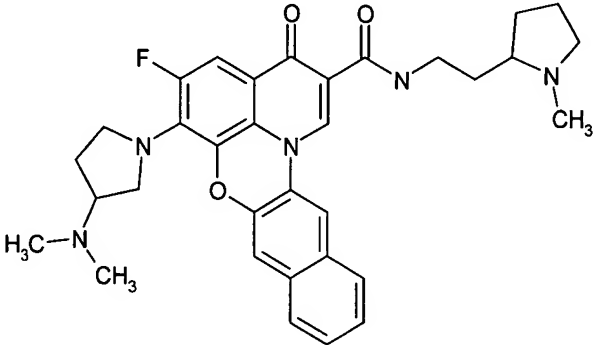
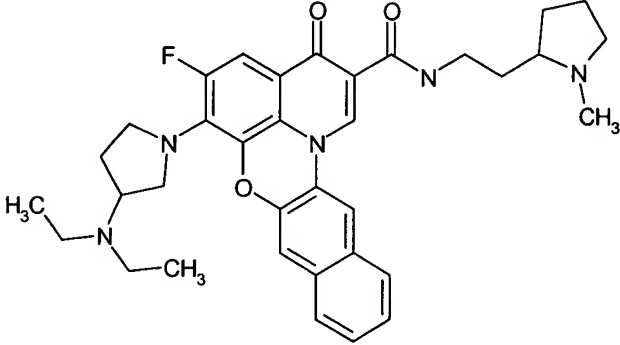


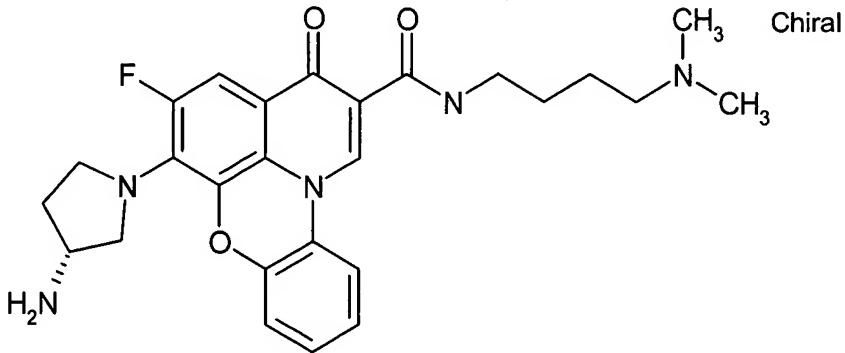
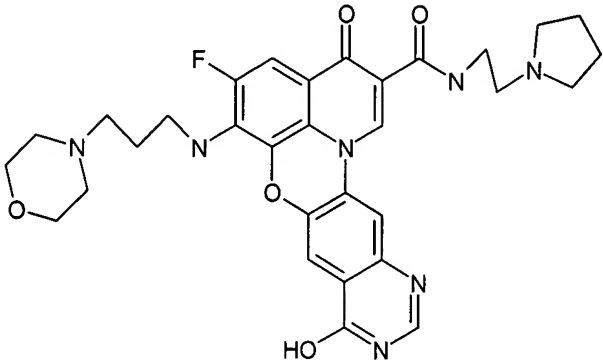
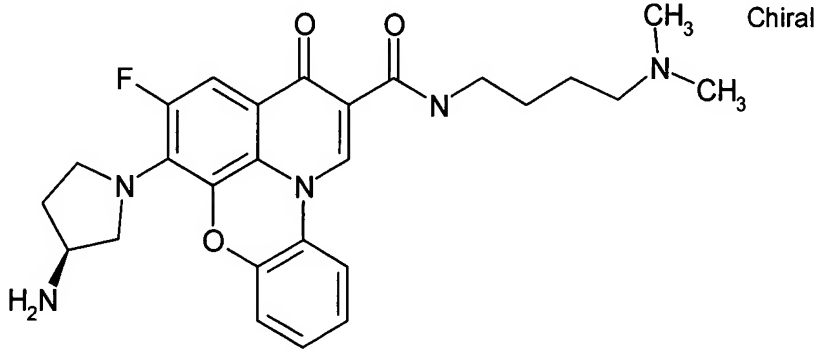
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
91		2.5	
92		2.5	
93		2.5	

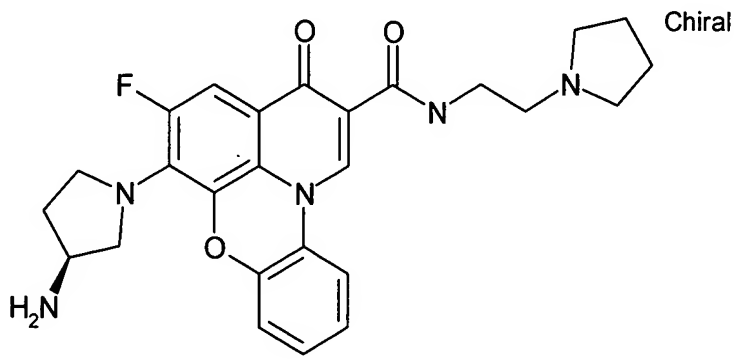
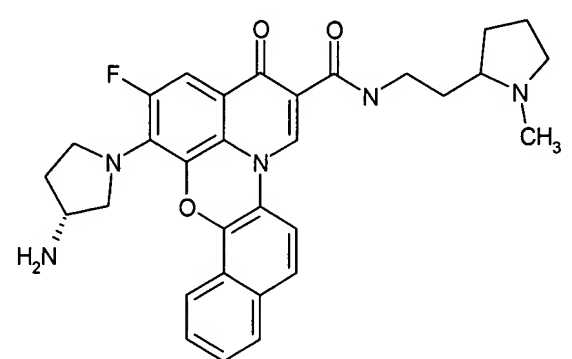
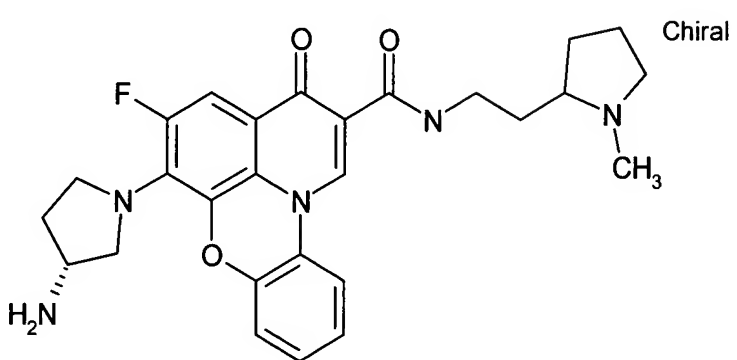
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
94		2.5	
95		2.5	
96		2.5	

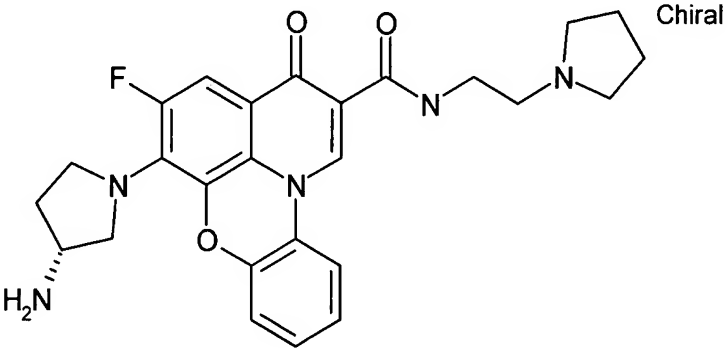
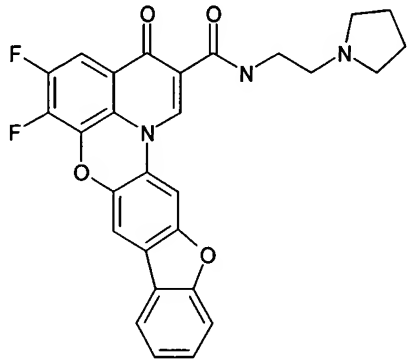
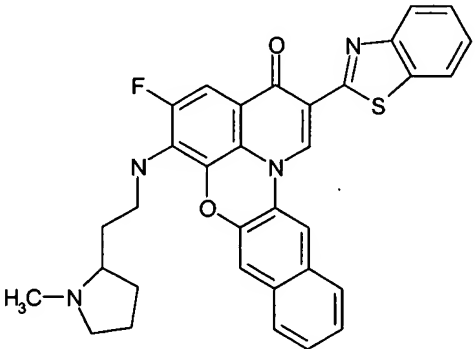
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
97		2.5	
98		2.5	
99		2.5	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
100		2.5	
101		2.25	
102		1.8	2.20

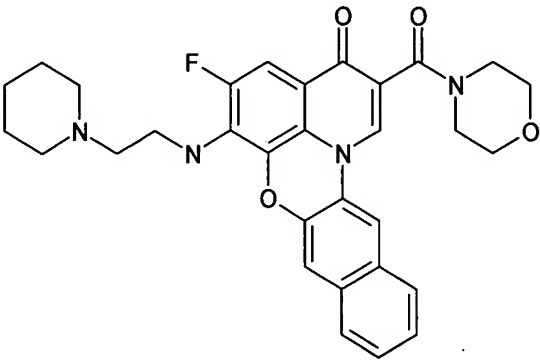
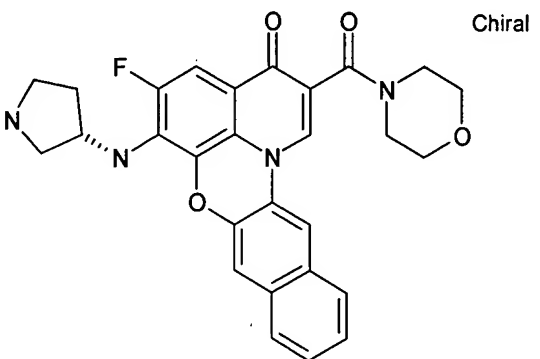
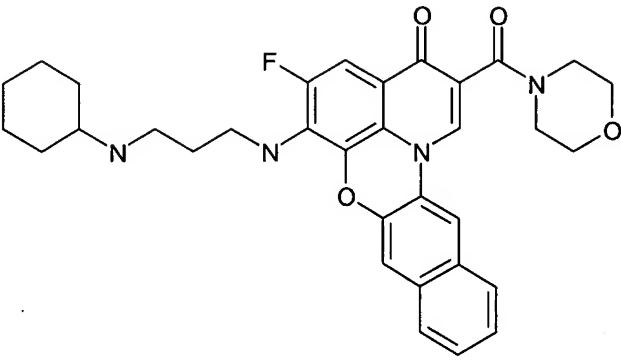
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
103		1.8	
104		1.75	2.80
105		1.75	2.80

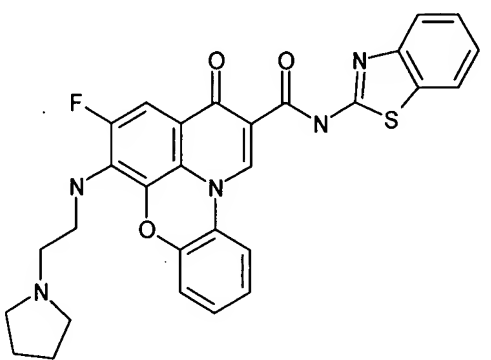
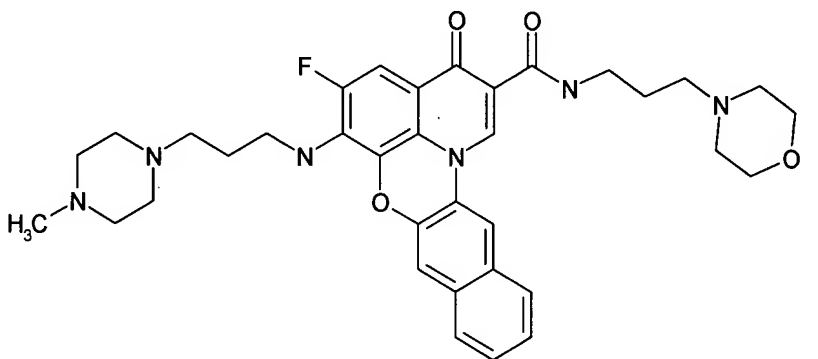
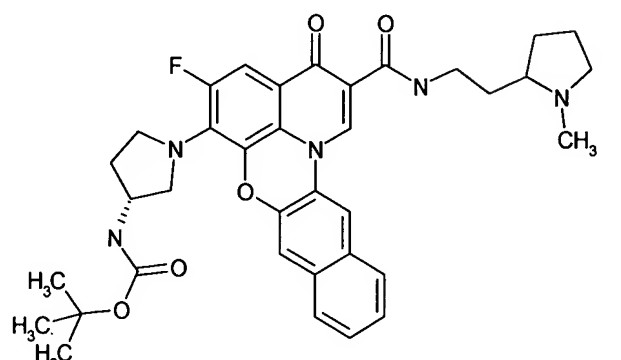
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
106		1.75	2.50
107		1.75	1.80
108		1.75	0.46

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
109		1.75	0.31
110		1.75	0.25
111		1.75	0.22

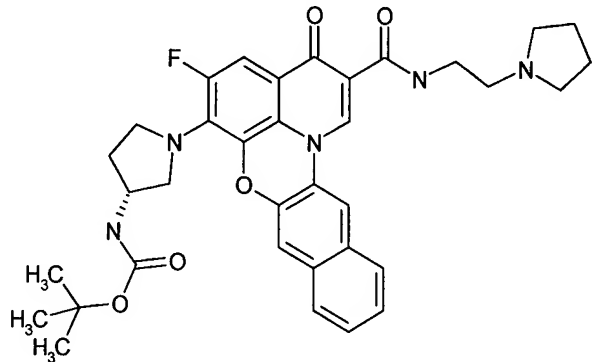
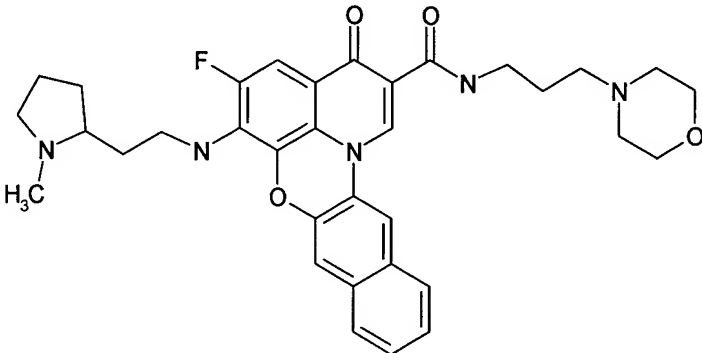
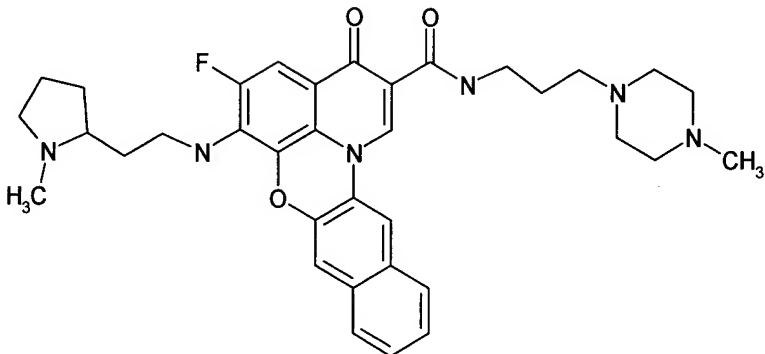
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
112		1.75	0.22
113		1.75	
114		1.75	

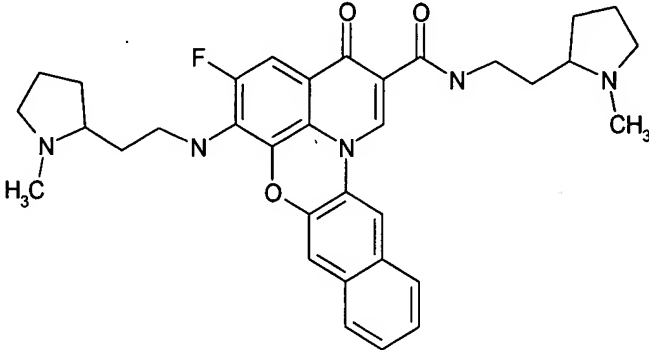
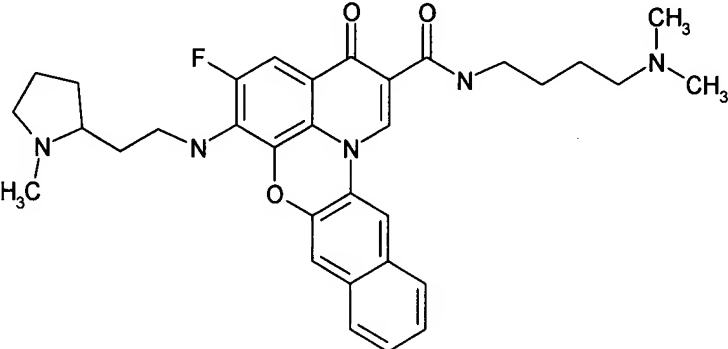
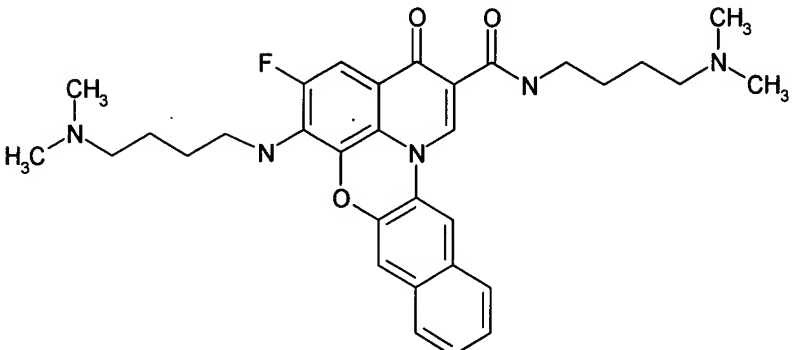


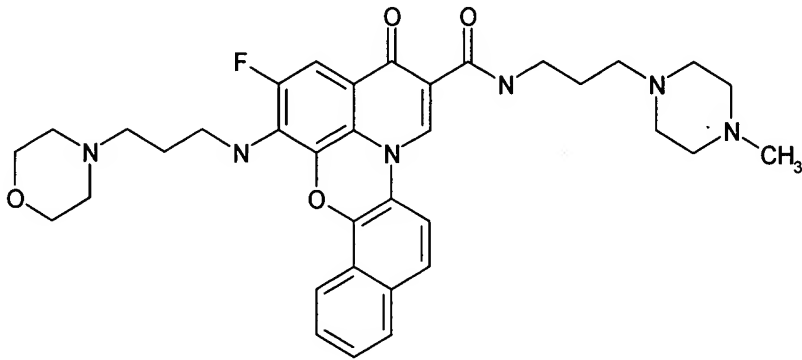
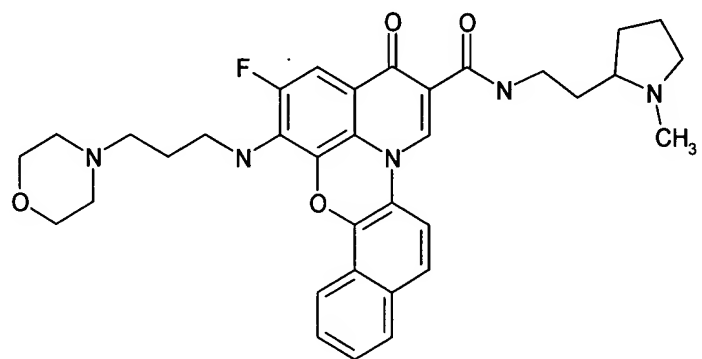
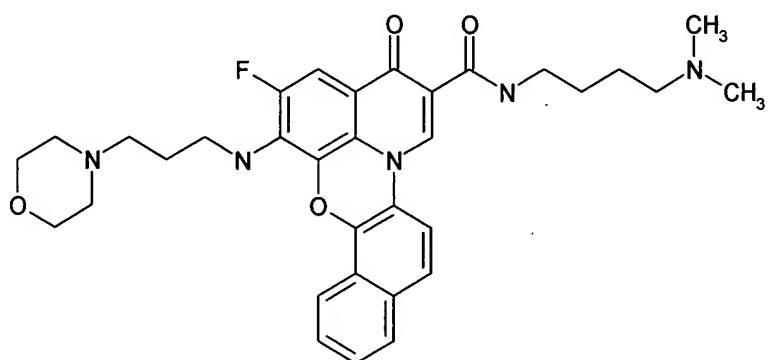
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
115		1.75	
116		1.75	
117		1.75	

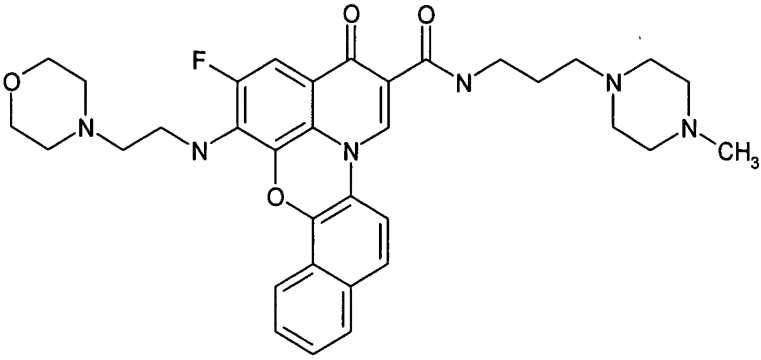
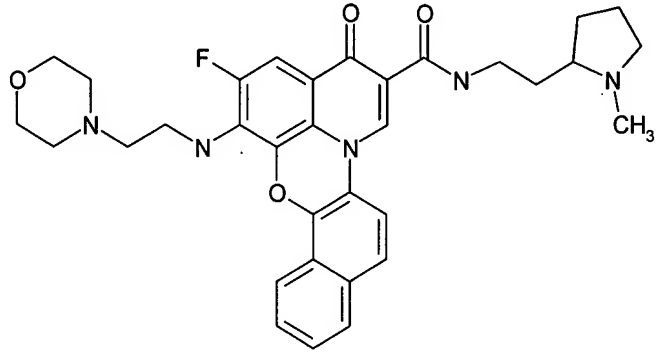
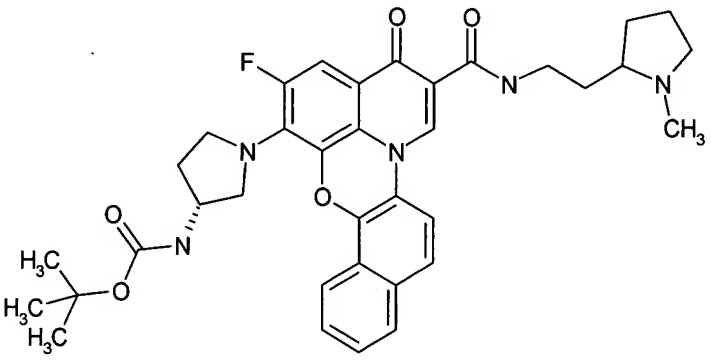
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
118		1.75	
119		1.75	
120		1.75	

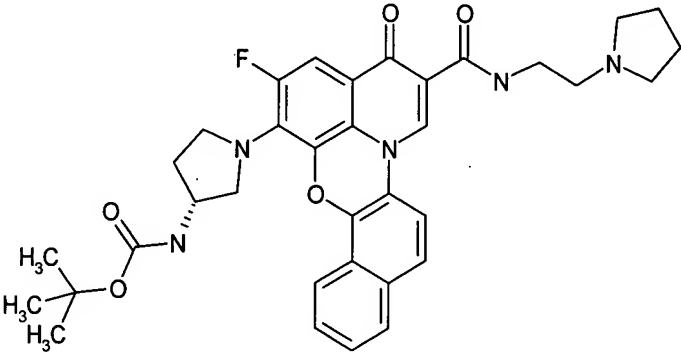
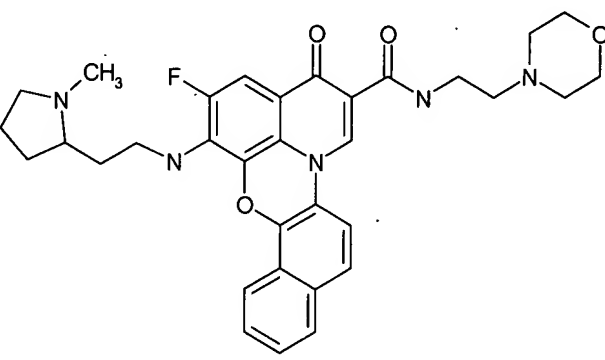
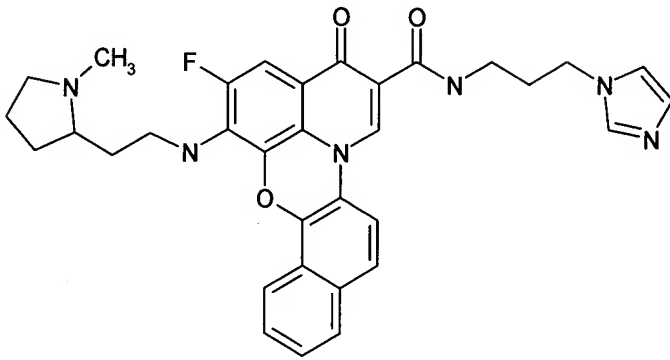
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	Structure	Stop Data c-Myc $\mu\text{M}$	MTS Data Hella $\mu\text{M}$
121		1.75	
122		1.75	
123		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
124		1.75	
125		1.75	
126		1.75	

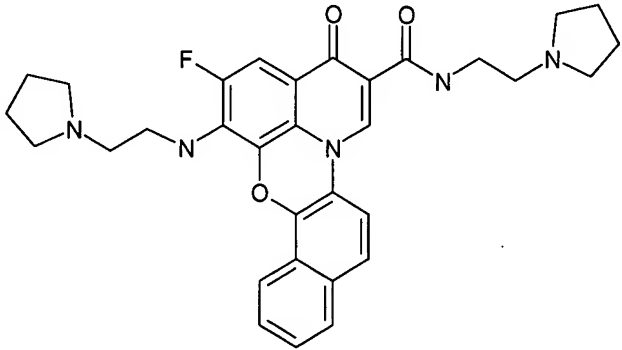
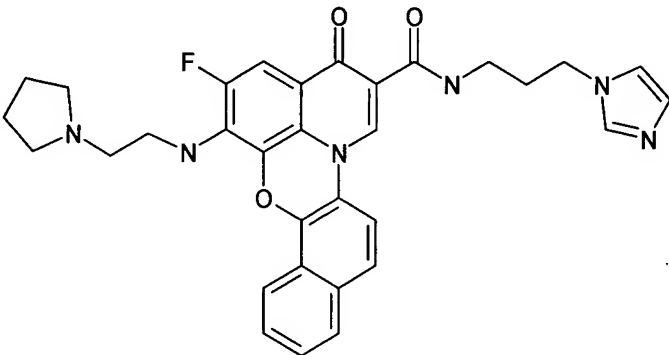
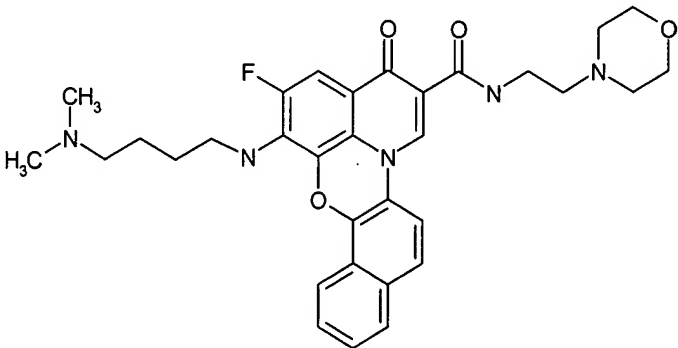
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
127		1.75	
128		1.75	
129		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
130		1.75	
131		1.75	
132		1.75	

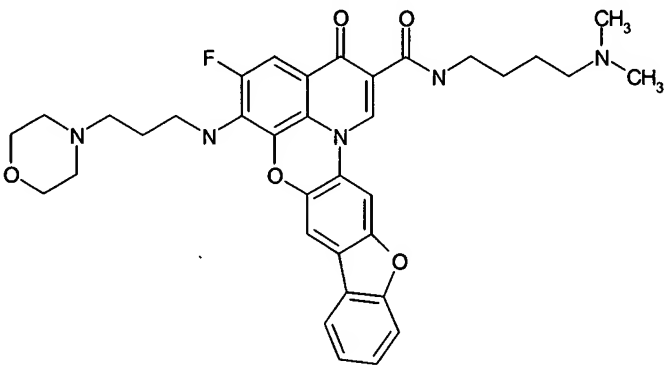
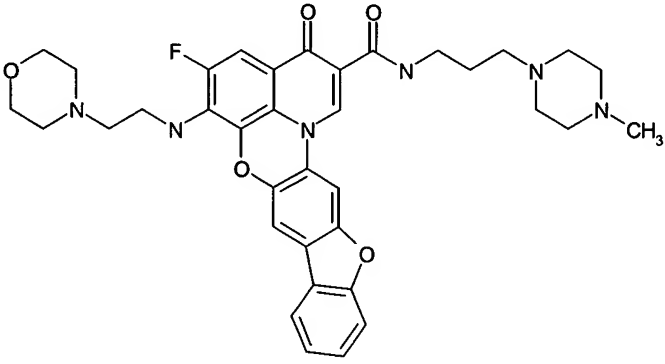
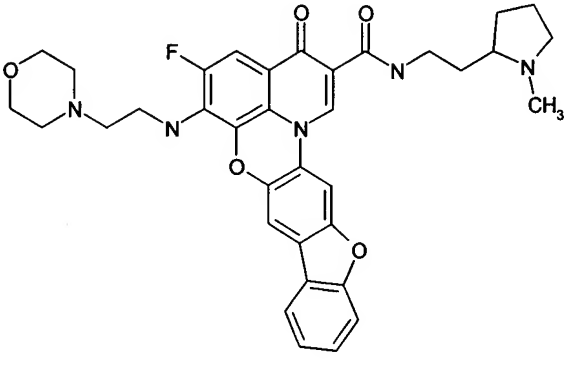
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
133		1.75	
134		1.75	
135		1.75	

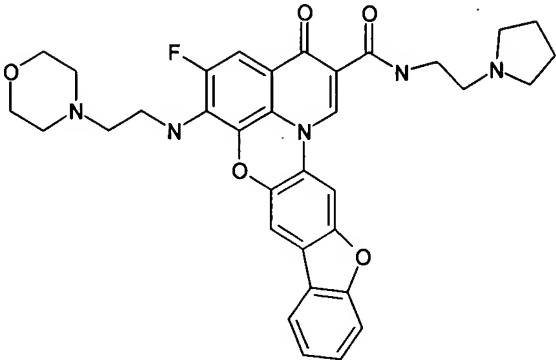
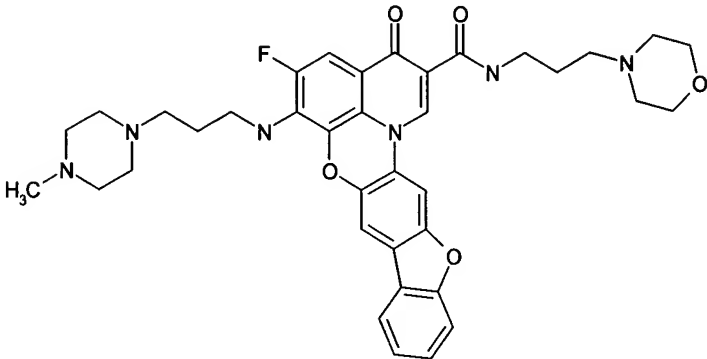
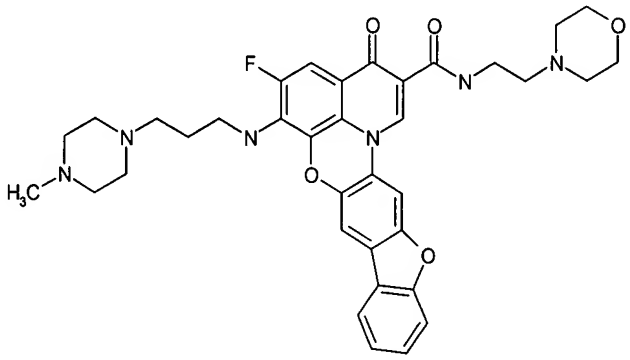
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
136		1.75	
137		1.75	
138		1.75	



	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
139		1.75	
140		1.75	
141		1.75	

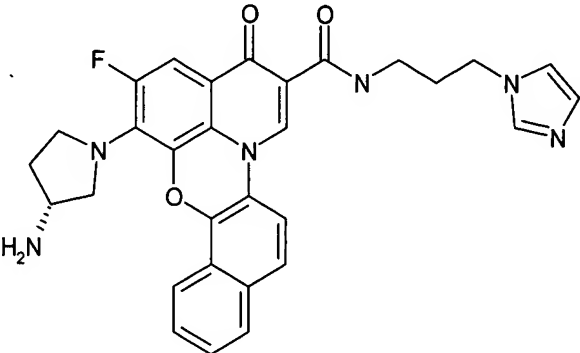
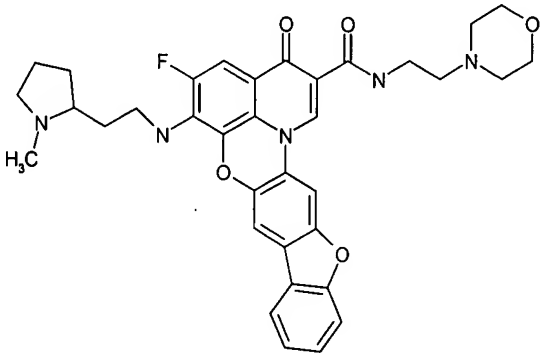
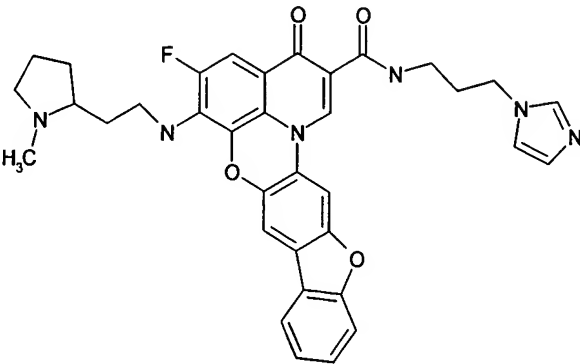
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
142		1.75	
143		1.75	
144		1.75	

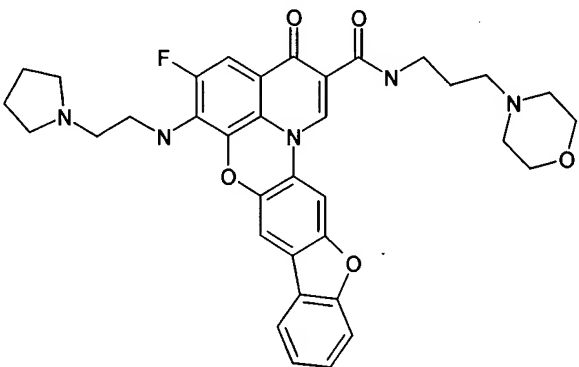
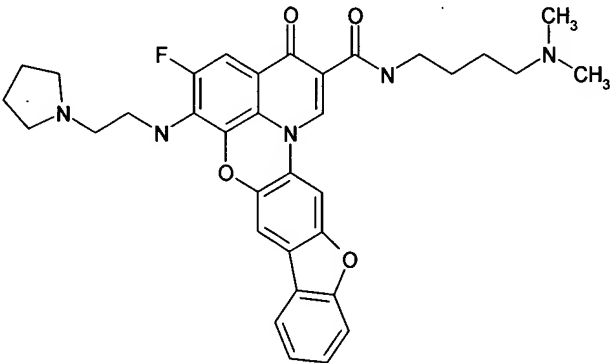
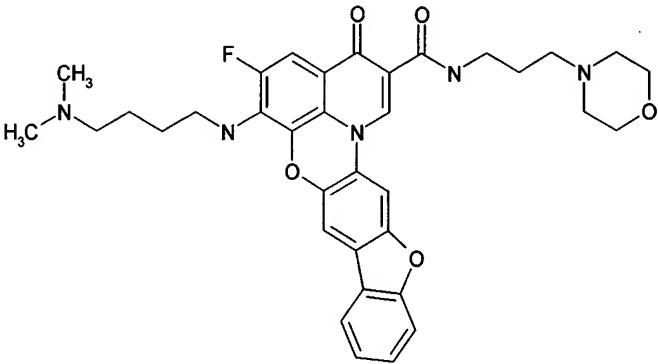
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
145		1.75	
146		1.75	
147		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
148		1.75	
149		1.75	
150		1.75	

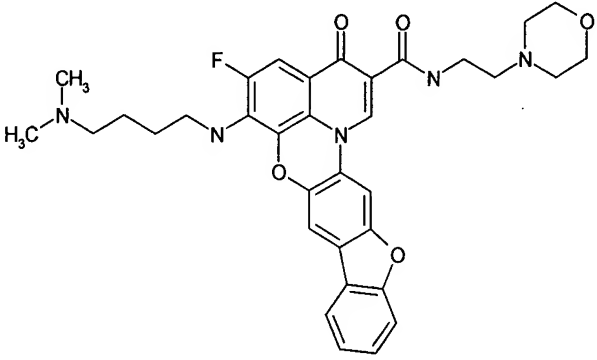
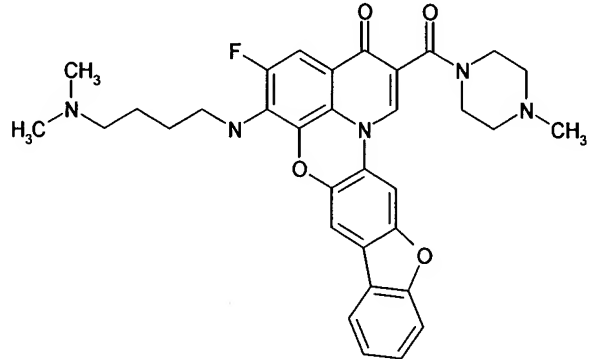
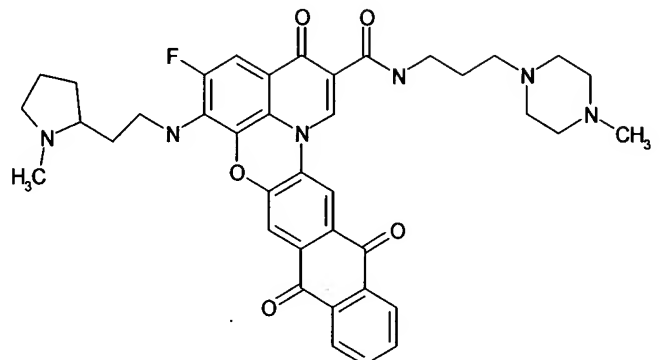
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
151		1.75	
152		1.75	
153		1.75	

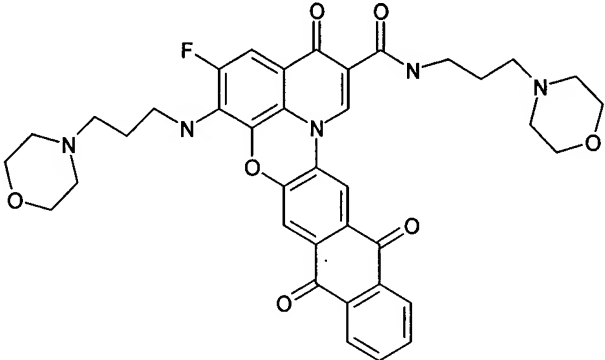
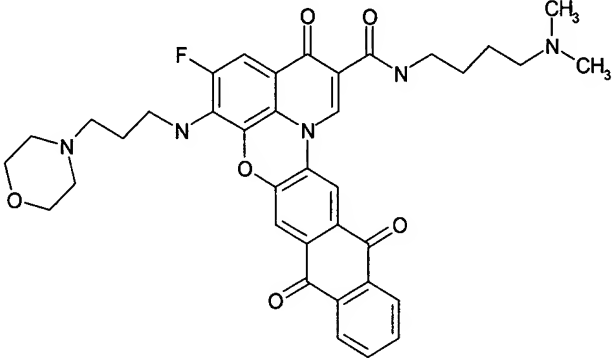
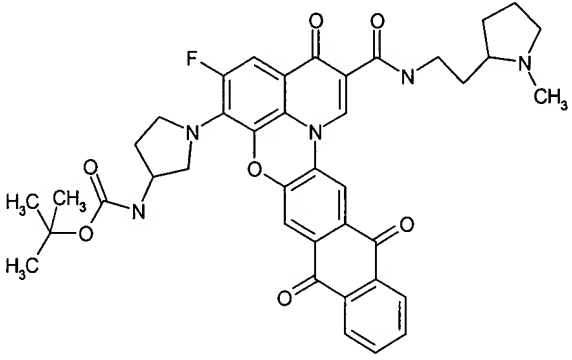
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
154		1.75	
155		1.75	
156		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
157		1.75	
158		1.75	
159		1.75	

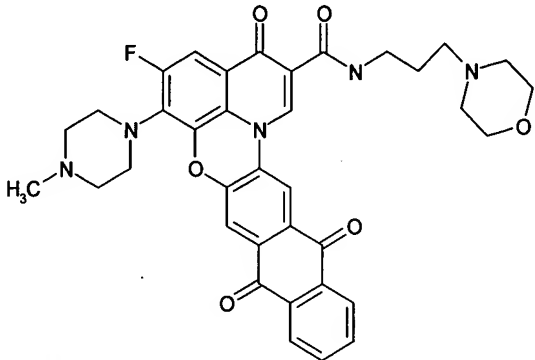
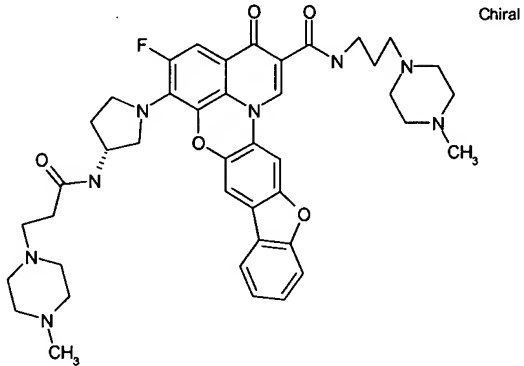
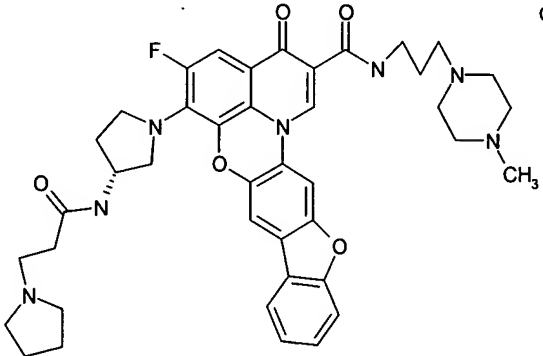
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
160		1.75	
161		1.75	
162		1.75	

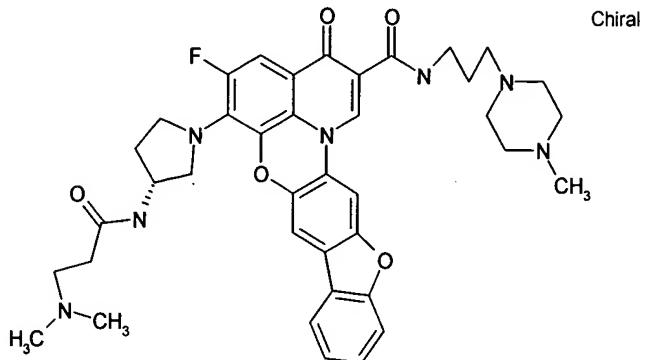
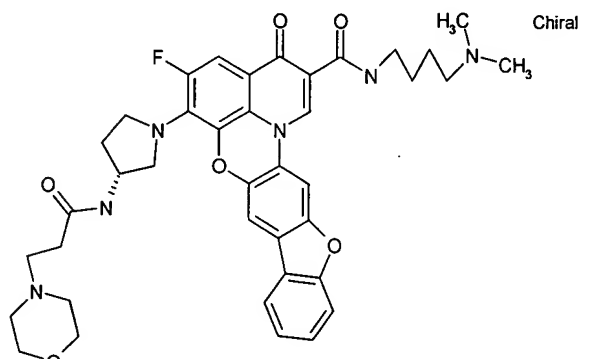
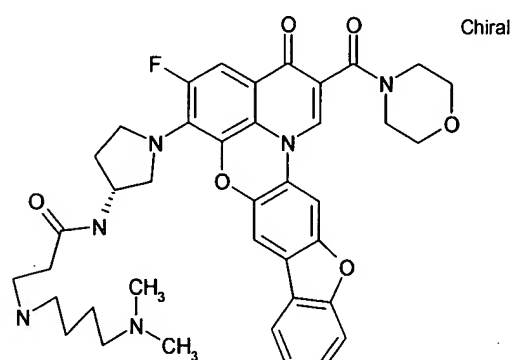


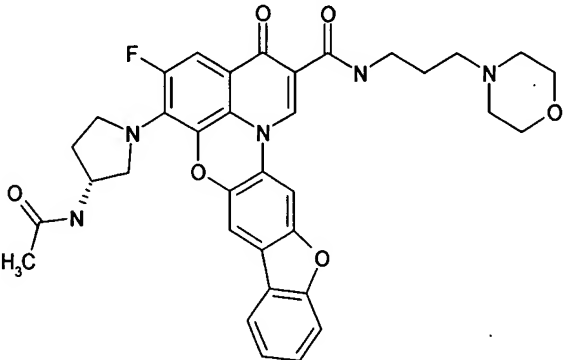
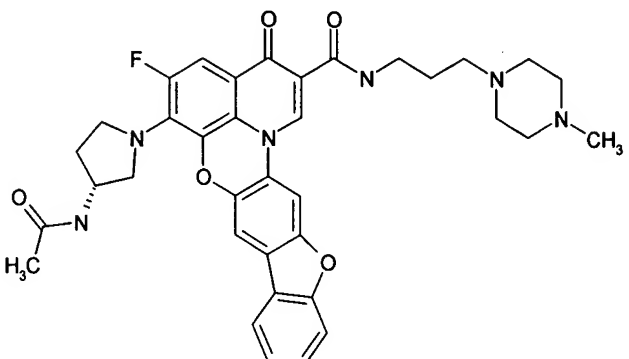
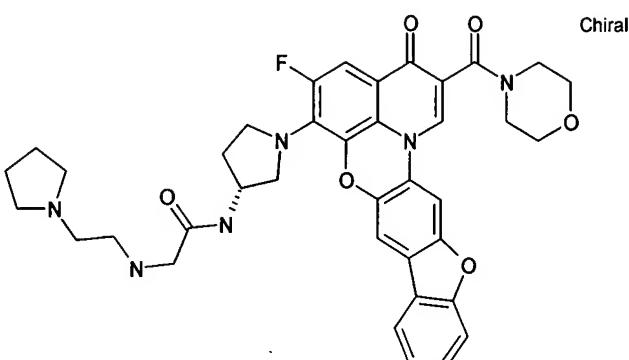
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
163		1.75	
164		1.75	
165		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
166		1.75	
167		1.75	
168		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
169		1.75	
170		1.75	
171		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
172		1.75	
173		1.75	
174		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
175	 <p>Chiral</p>	1.75	
176	 <p>Chiral</p>	1.75	
177	 <p>Chiral</p>	1.75	

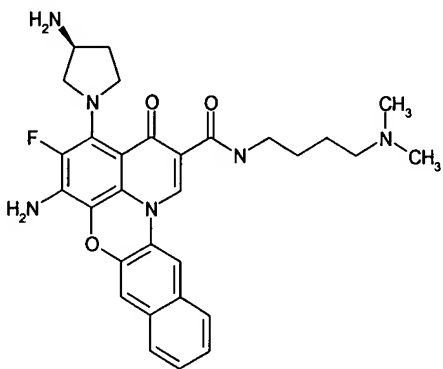
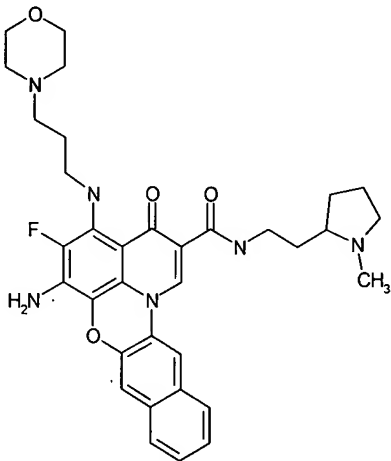
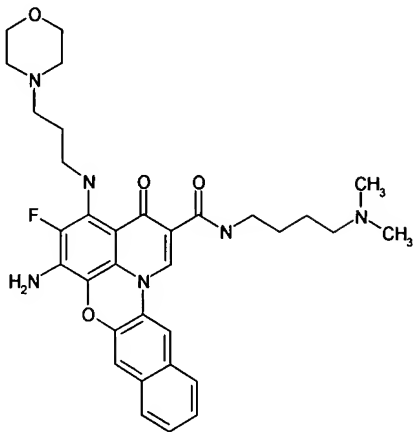
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
178		1.75	
179		1.75	
180		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
181		1.75	
182		1.75	
183		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
184		1.75	
185		1.75	
186		1.75	



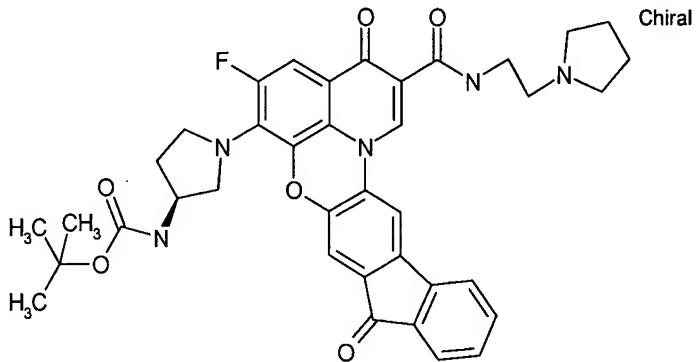
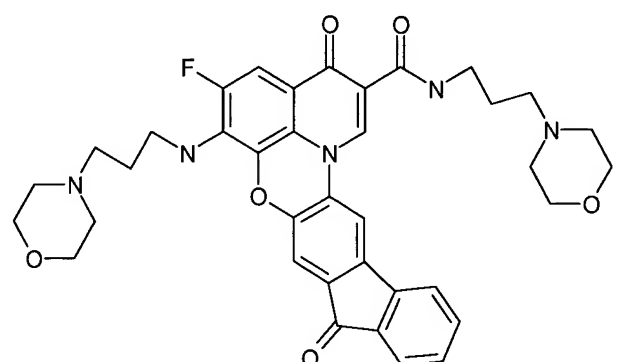
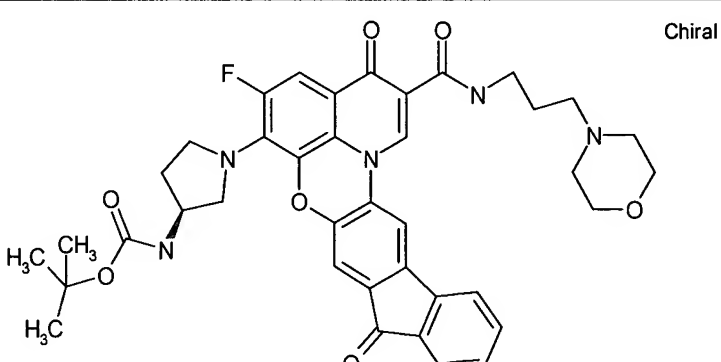
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
187		1.75	
188		1.75	
189		1.75	

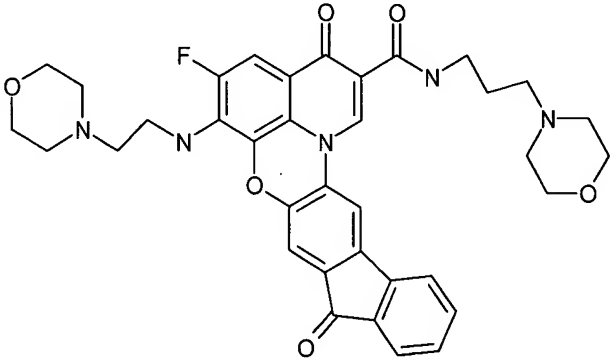
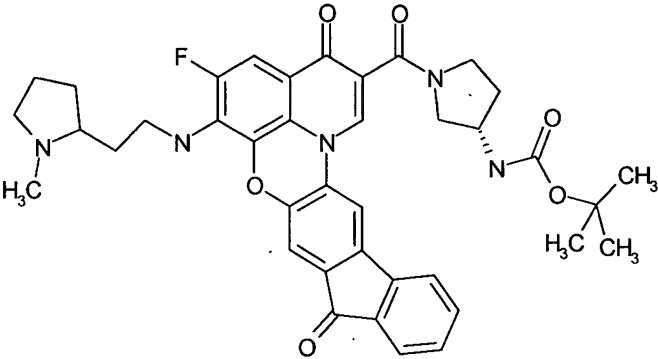
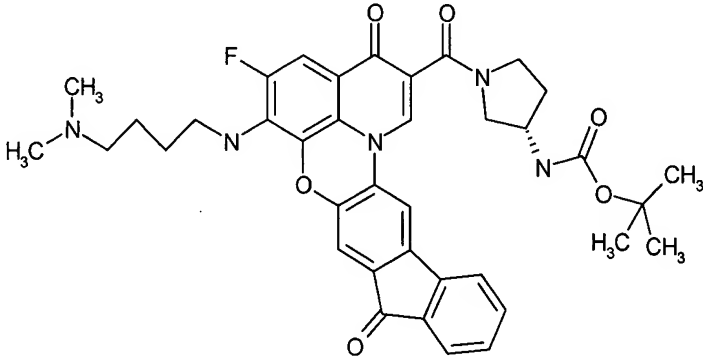
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
190		1.75	
191		1.75	
192		1.75	

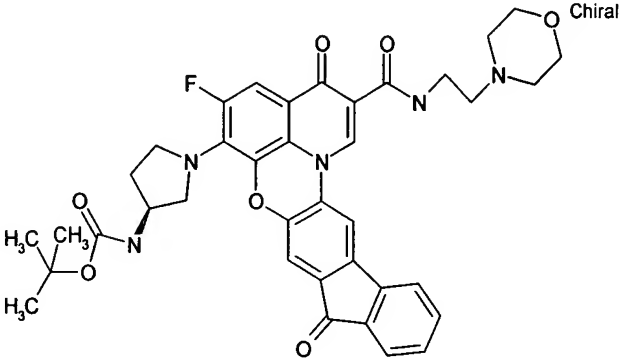
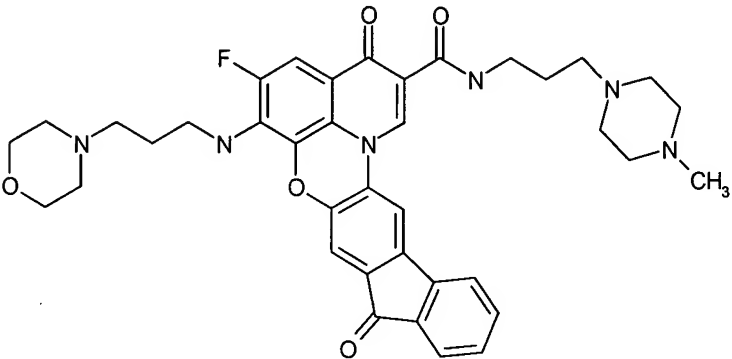
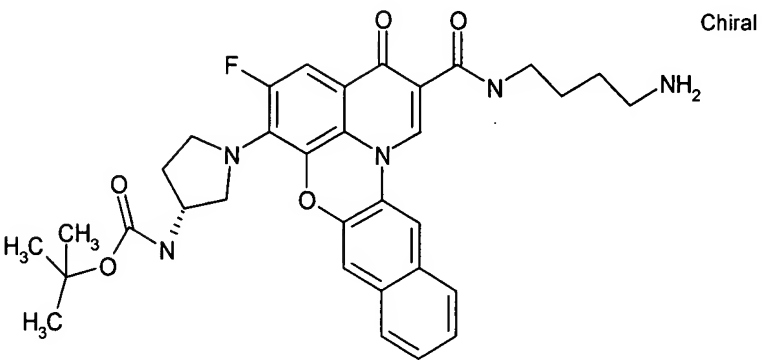
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
193		1.75	
194		1.75	
195		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
196		1.75	
197		1.75	
198		1.75	

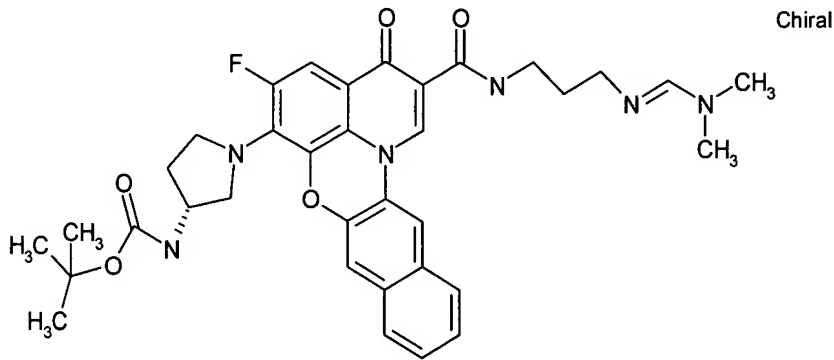
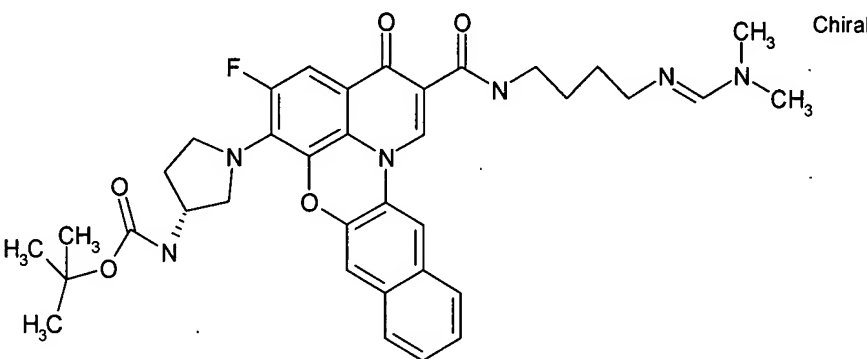
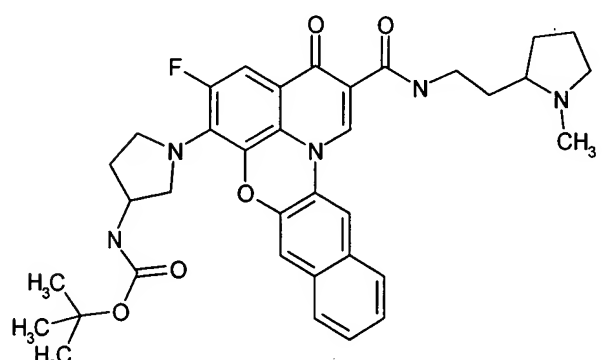
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
199		1.75	
200		1.75	
201		1.75	

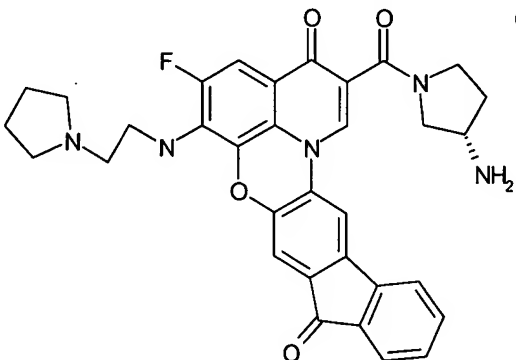
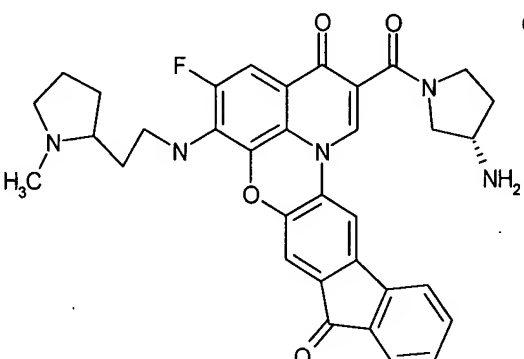
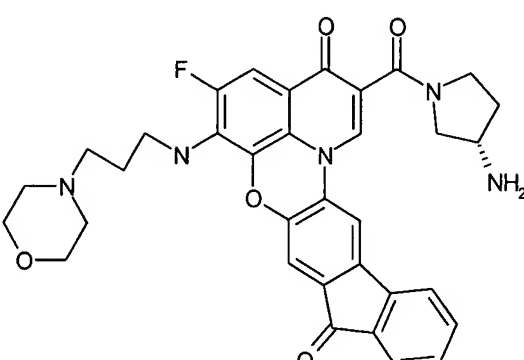
	Structure	Stop Data c-Myc $\mu\text{M}$	MTS Data Hella $\mu\text{M}$
202	 <p>Chiral</p>	1.75	
203		1.75	
204	 <p>Chiral</p>	1.75	

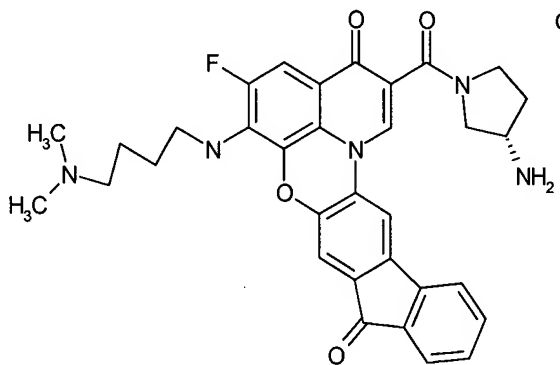
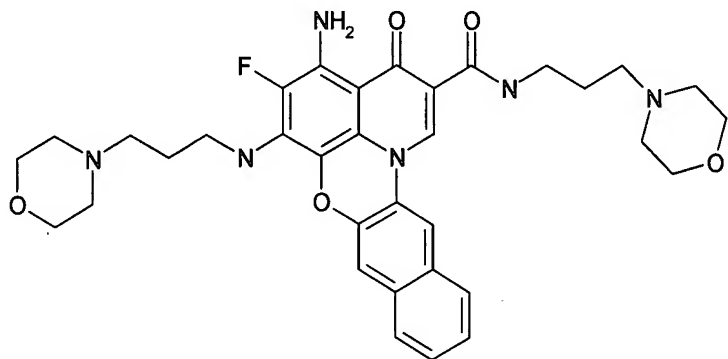
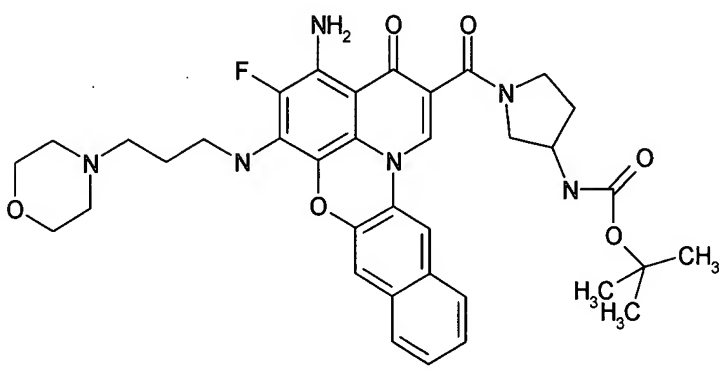
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
205		1.75	
206	<p>Chiral</p> 	1.75	
207	<p>Chiral</p> 	1.75	

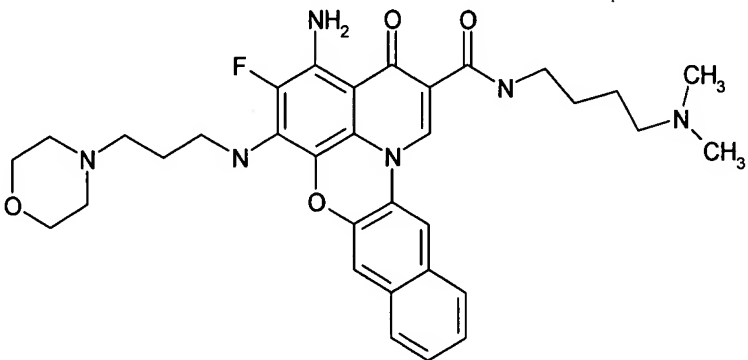
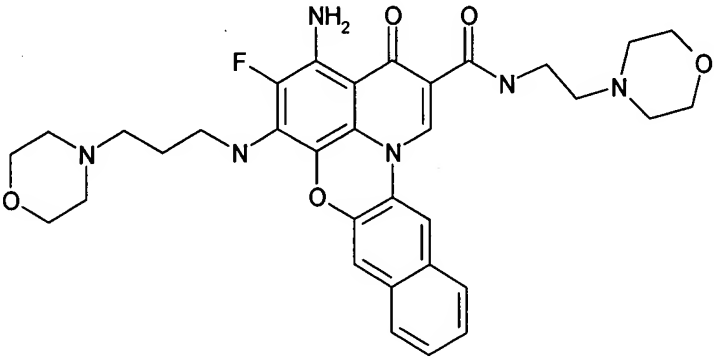
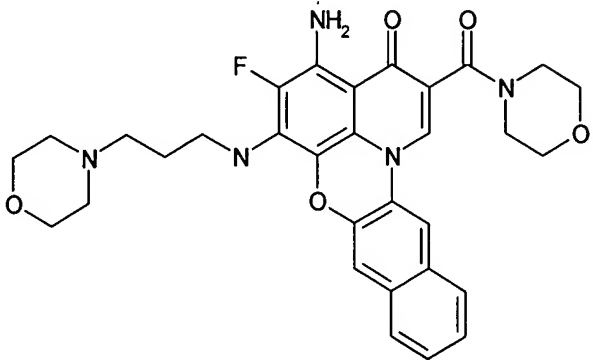
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
208		1.75	
209		1.75	
210		1.75	

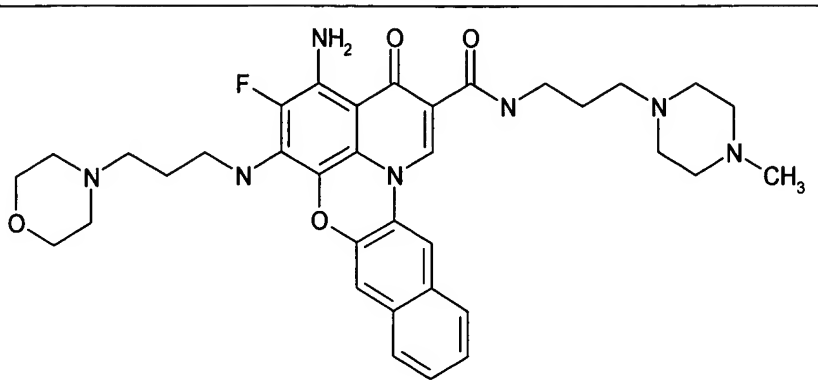
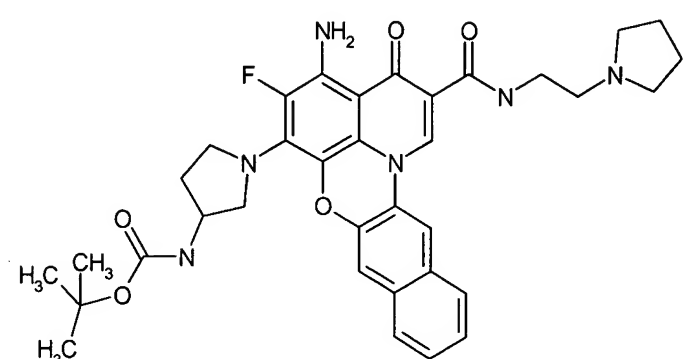
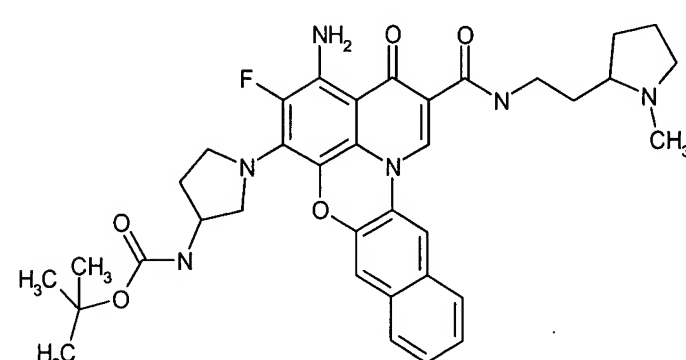


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
211	 <p style="text-align: right;">Chiral</p>	1.75	
212	 <p style="text-align: right;">Chiral</p>	1.75	
213		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
214	<p>Chiral</p> 	1.75	
215	<p>Chiral</p> 	1.75	
216	<p>Chiral</p> 	1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
217	<p>Chiral</p> 	1.75	
218		1.75	
219		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
220		1.75	
221		1.75	
222		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
223		1.75	
224		1.75	
225		1.75	

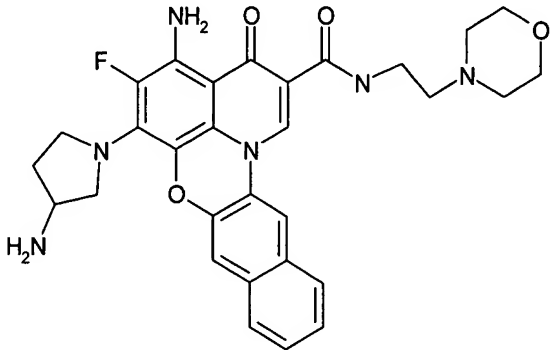
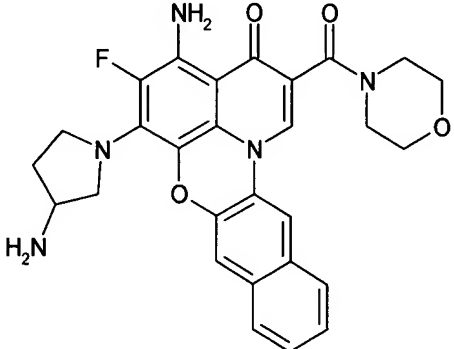
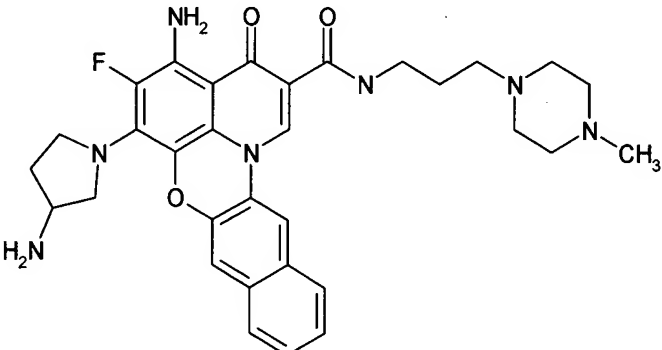
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
226		1.75	
227		1.75	
228		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
229		1.75	
230		1.75	
231		1.75	

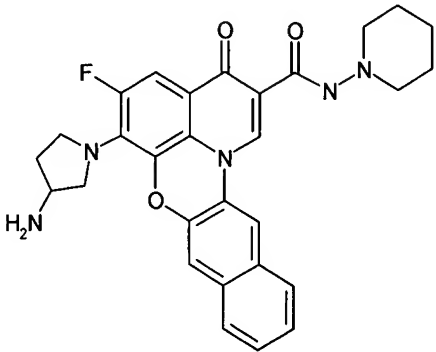
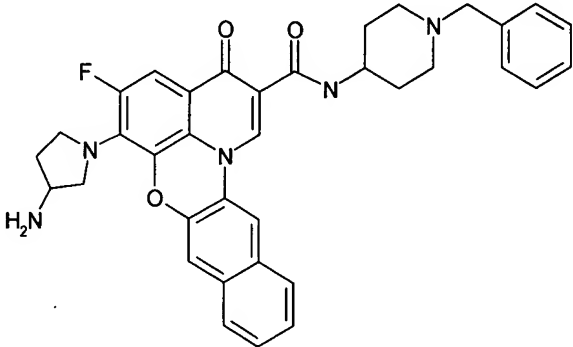
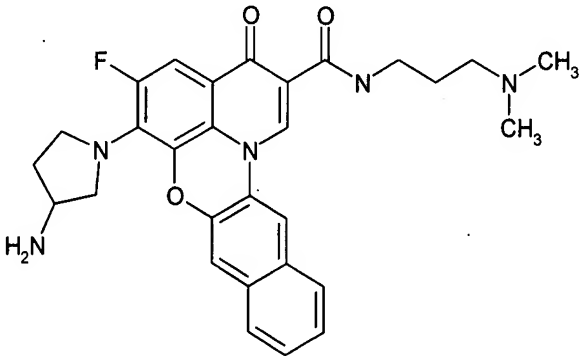
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
232		1.75	
233		1.75	
234		1.75	



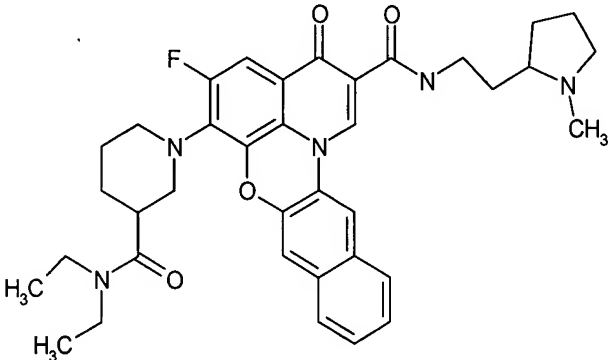
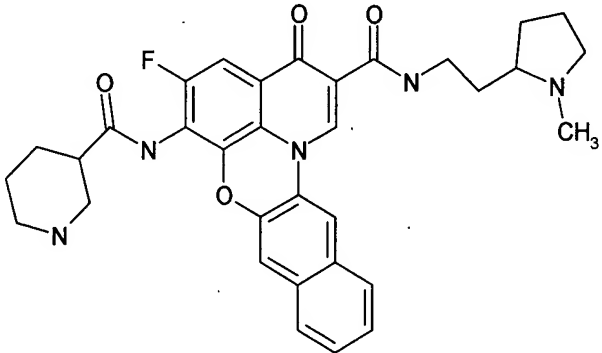
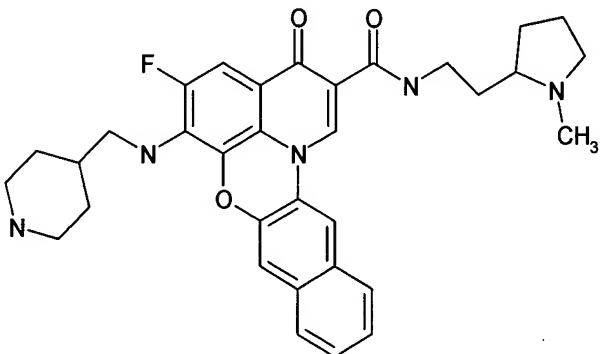
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
235		1.75	
236		1.75	
237		1.75	

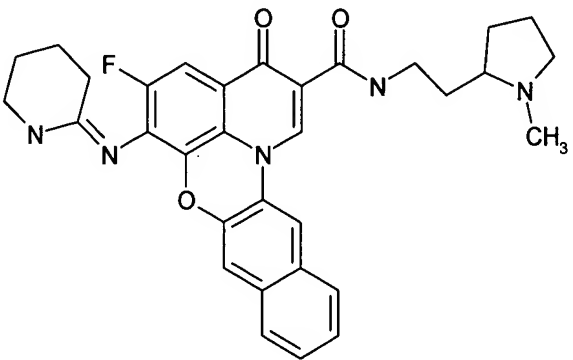
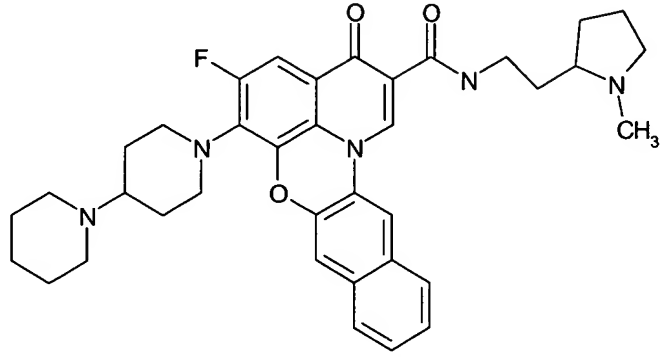
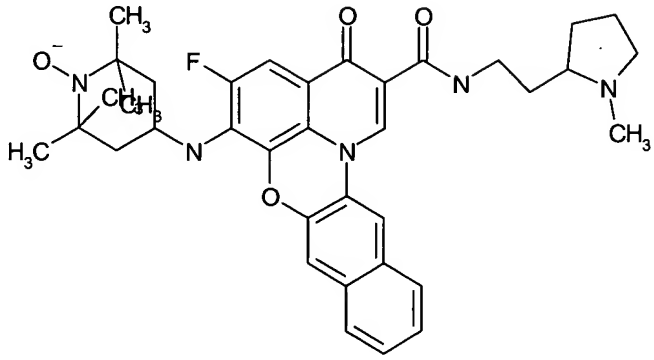
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
238		1.75	
239		1.75	
240		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
241		1.75	
242		1.75	
243		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
244		1.75	
245		1.75	
246		1.75	

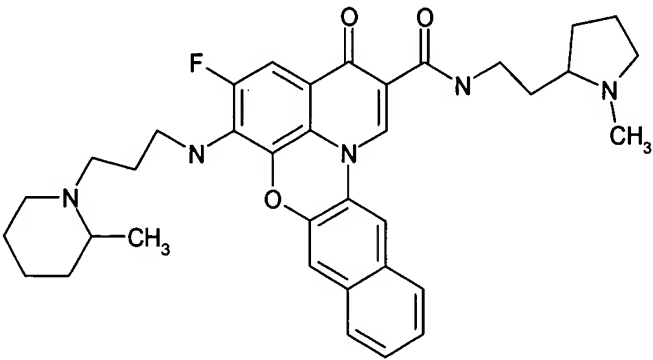
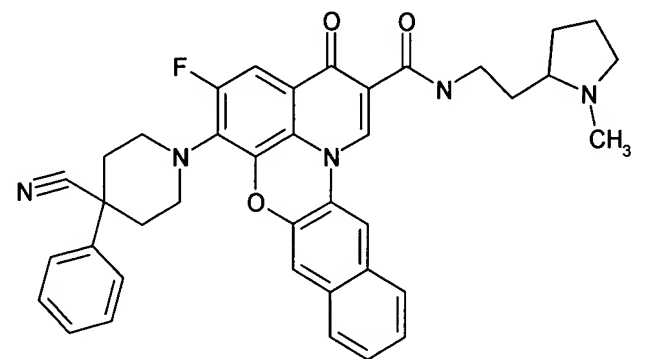
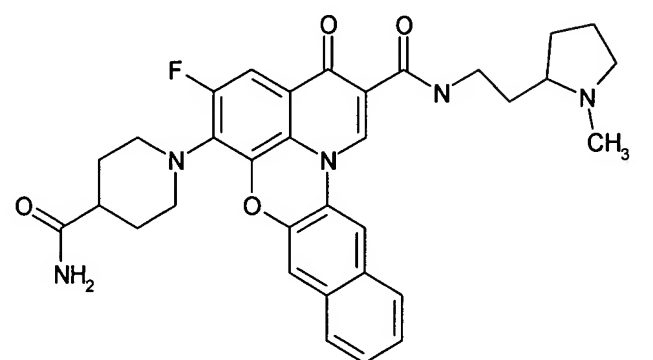
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
247		1.75	
248		1.75	
249		1.75	

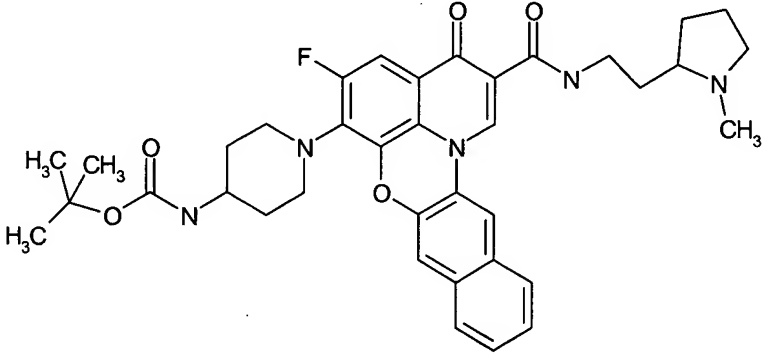
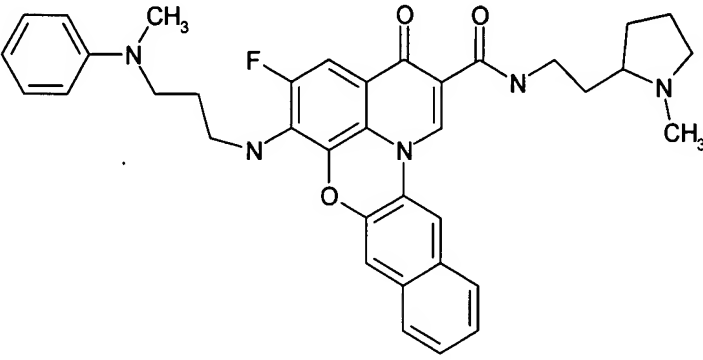
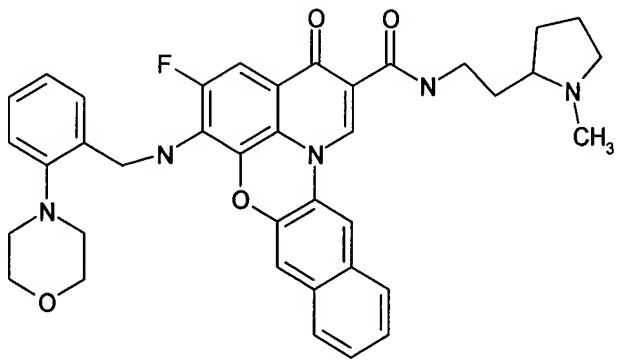
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
250		1.75	
251		1.75	
252		1.75	

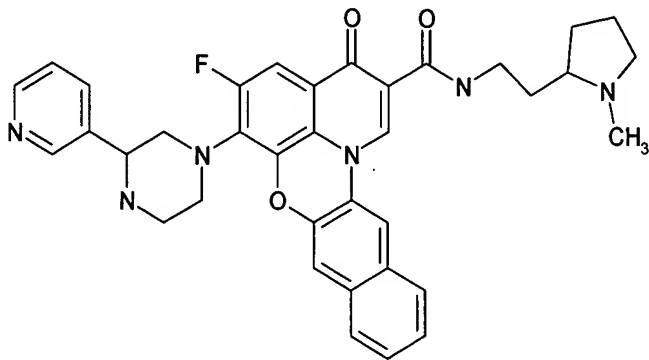
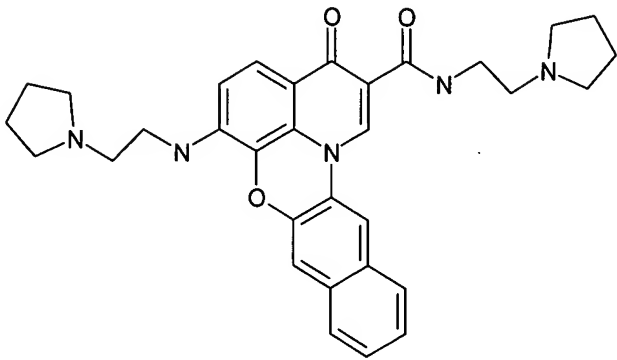
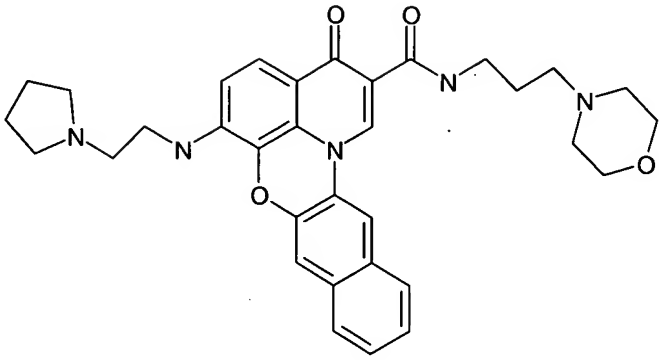
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
253		1.75	
254		1.75	
255		1.75	

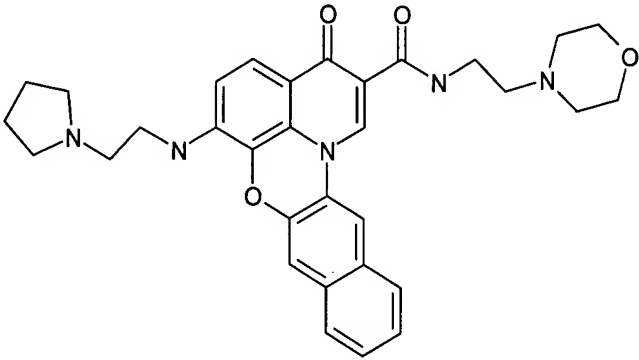
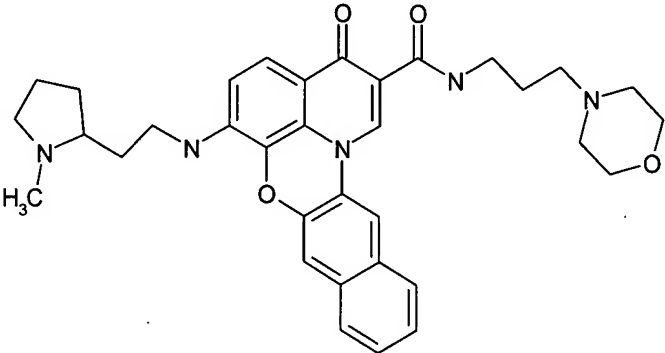
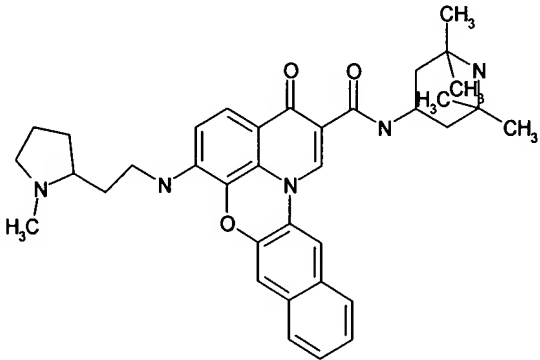
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
256		1.75	
257		1.75	
258		1.75	

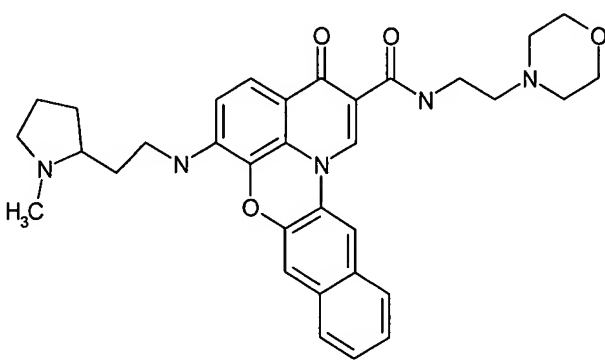
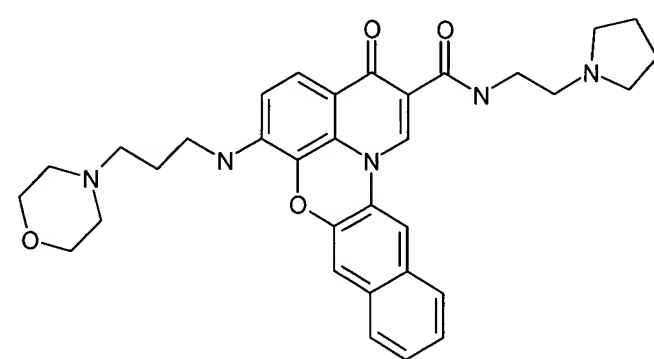
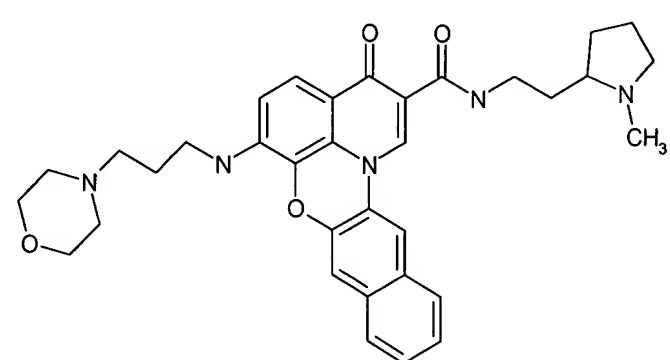


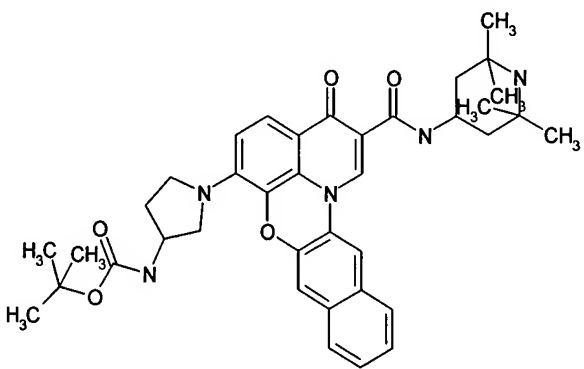
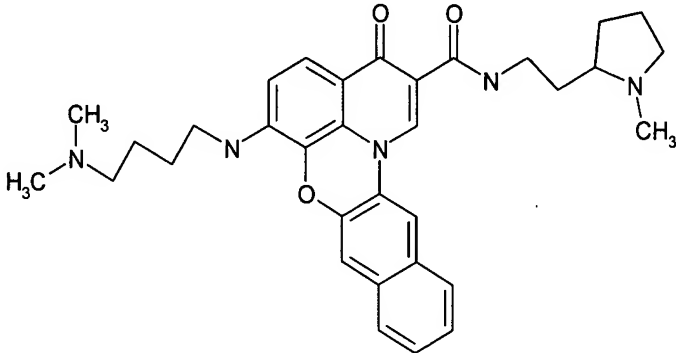
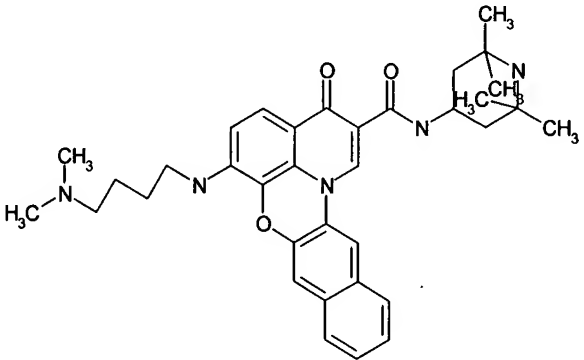
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
259		1.75	
260		1.75	
261		1.75	

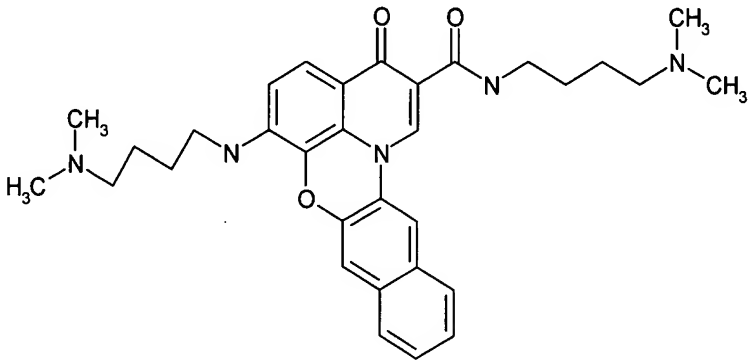
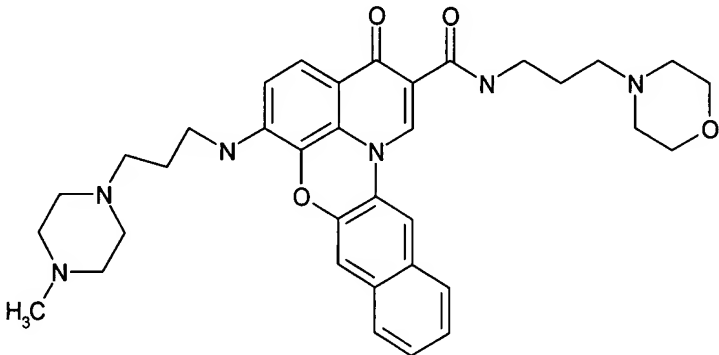
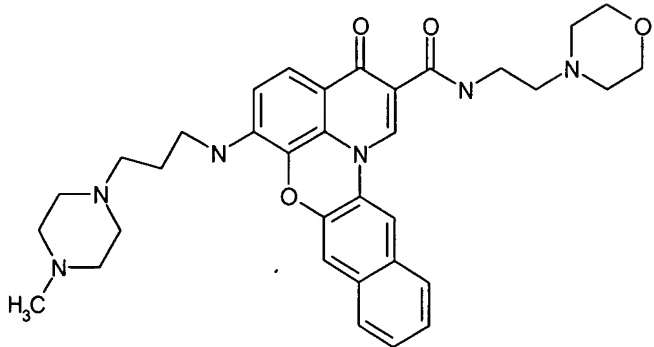
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
262		1.75	
263		1.75	
264		1.75	

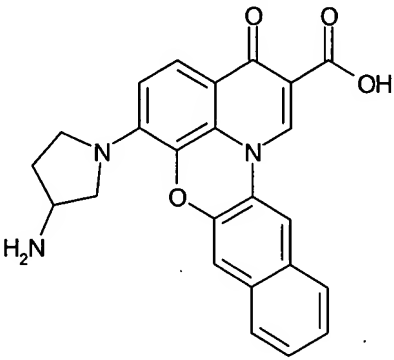
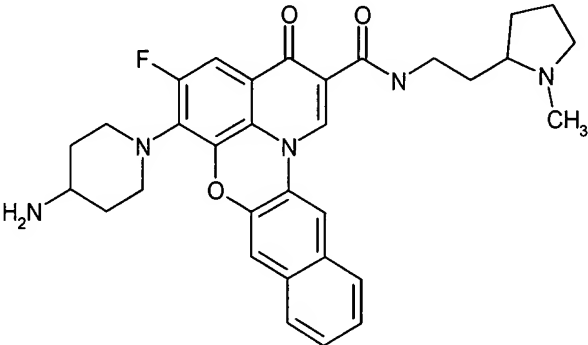
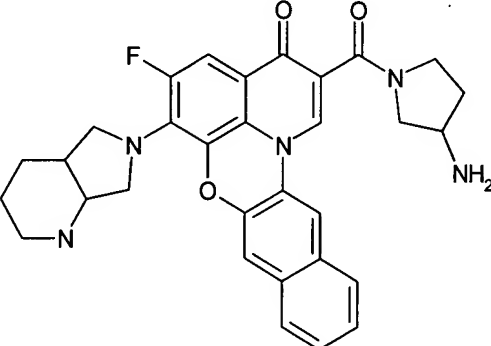
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
265		1.75	
266		1.75	
267		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
268		1.75	
269		1.75	
270		1.75	

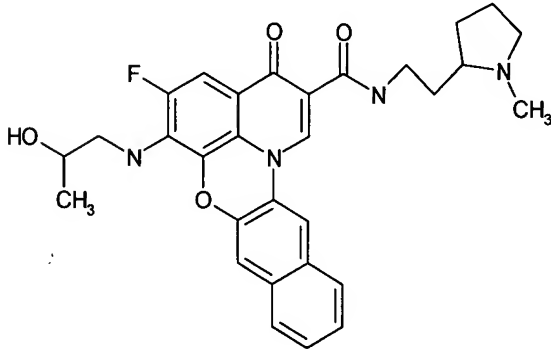
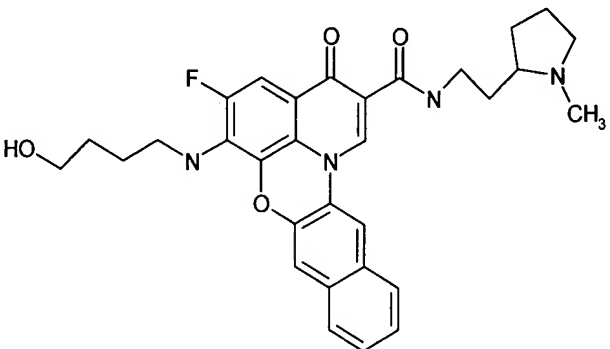
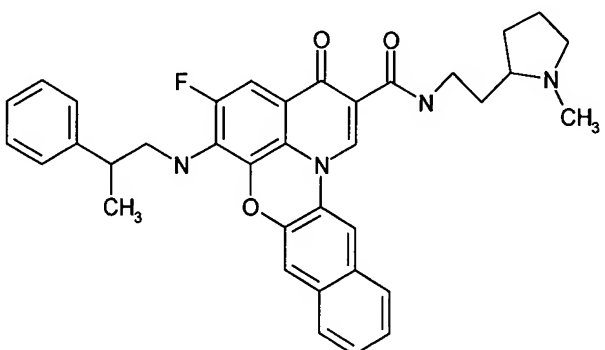
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
271		1.75	
272		1.75	
273		1.75	

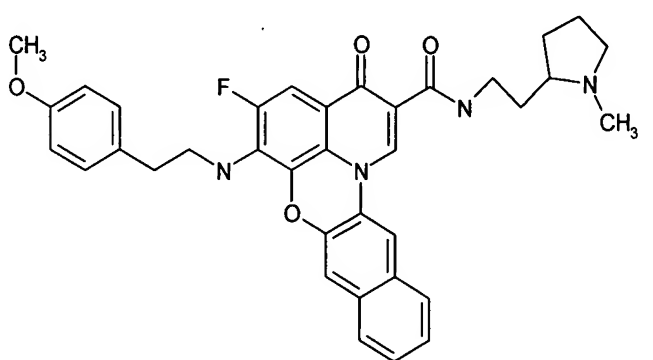
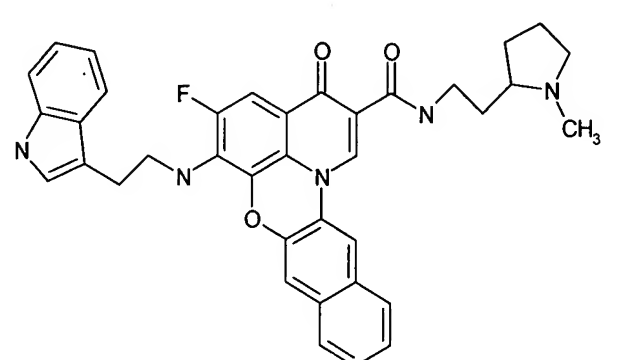
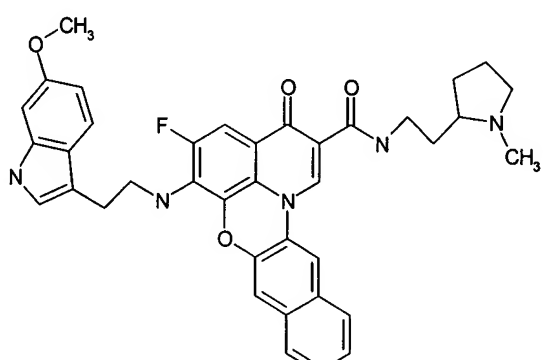
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
274		1.75	
275		1.75	
276		1.75	

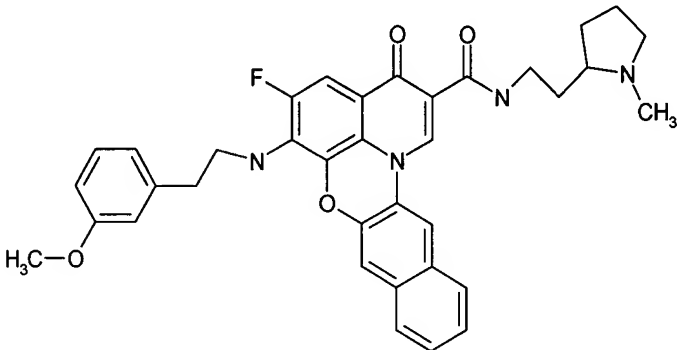
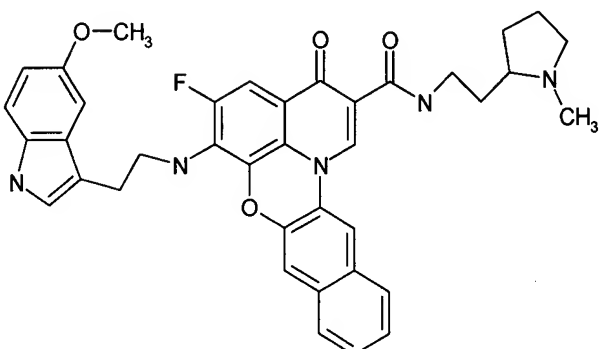
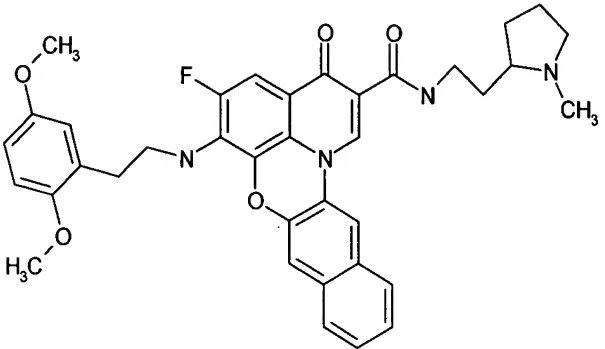
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
277		1.75	
278		1.75	
279		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
280		1.75	
281		1.75	
282		1.75	

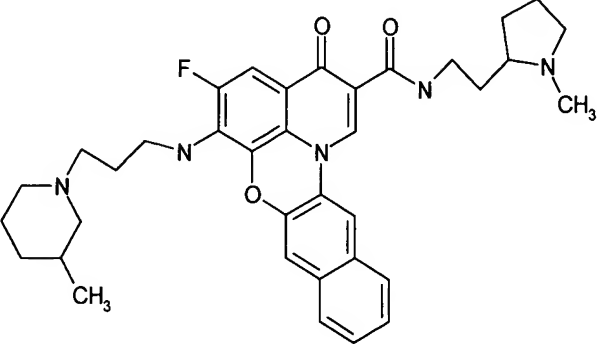
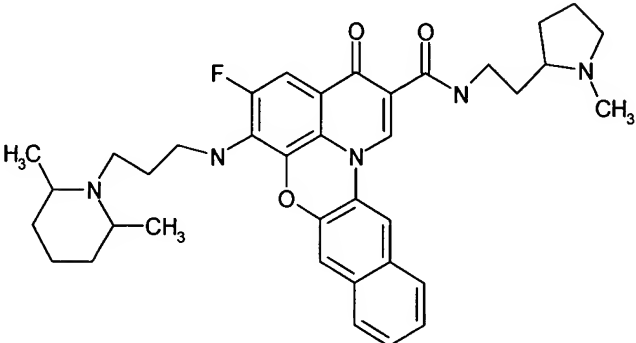
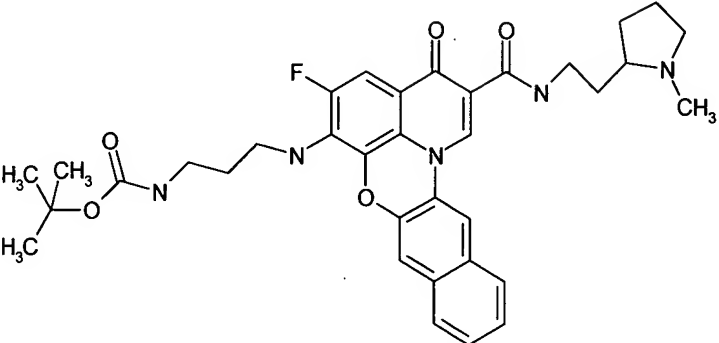


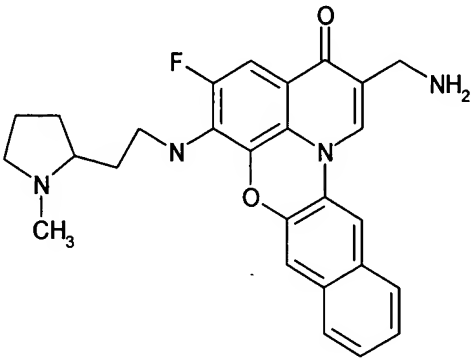
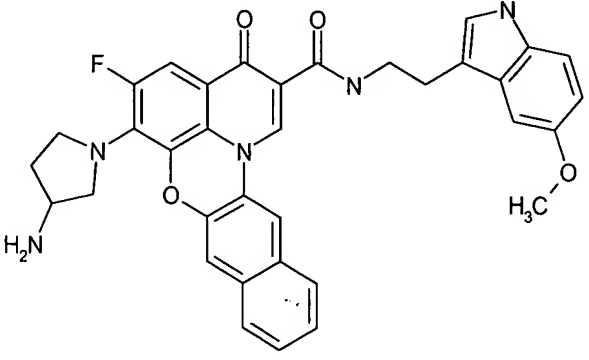
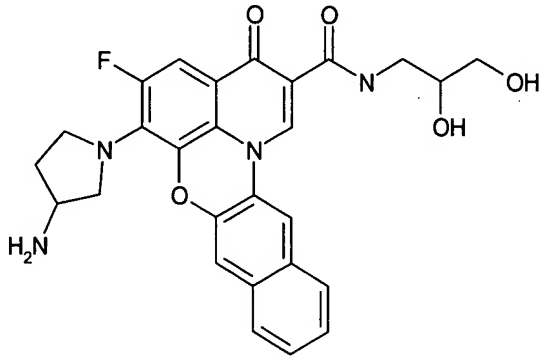
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
283		1.75	
284		1.75	
285		1.75	

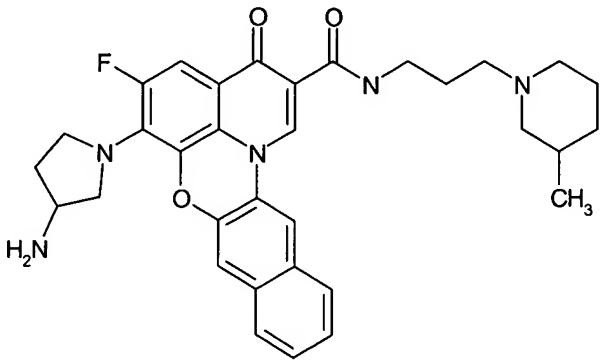
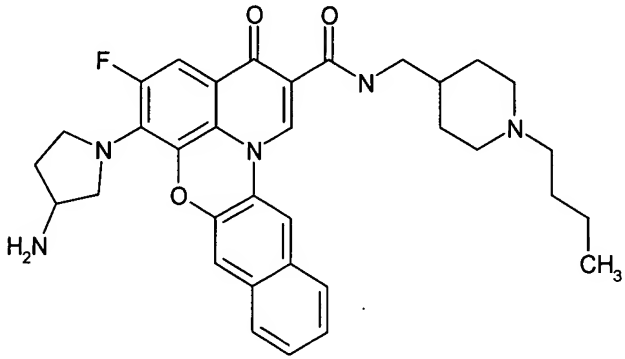
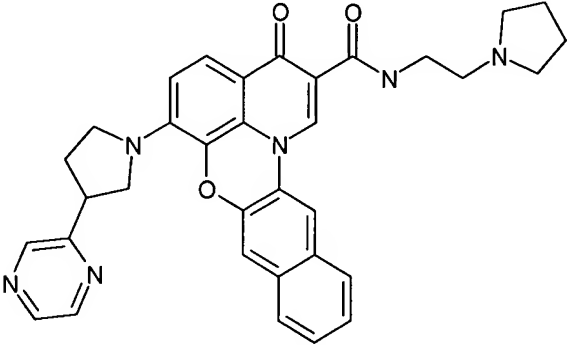
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
286		1.75	
287		1.75	
288		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
289		1.75	
290		1.75	
291		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
292		1.75	
293		1.75	
294		1.75	

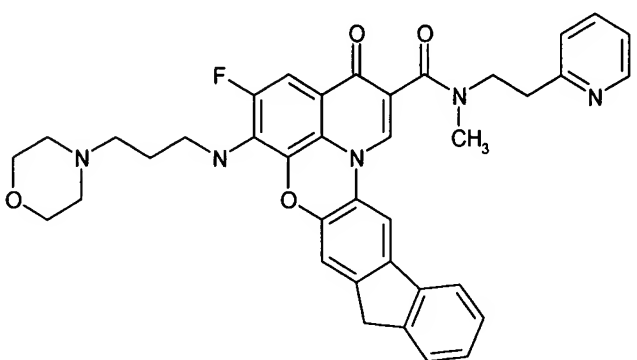
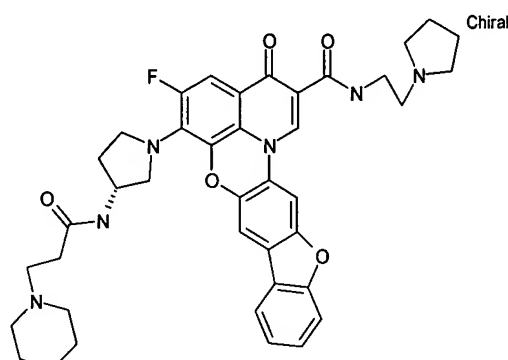
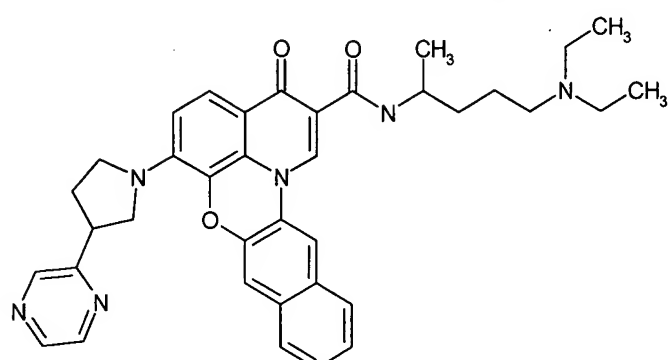
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
295		1.75	
296		1.75	
297		1.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
298		1.75	
299		1.75	
300		1.75	

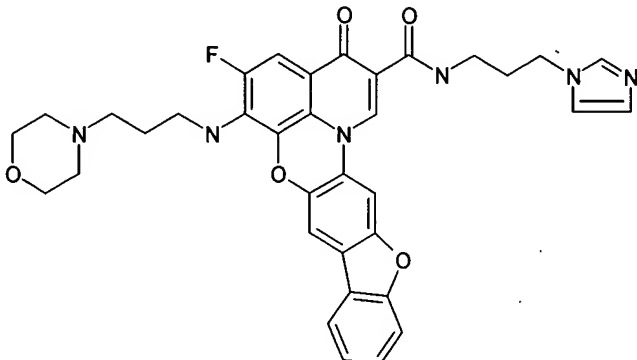
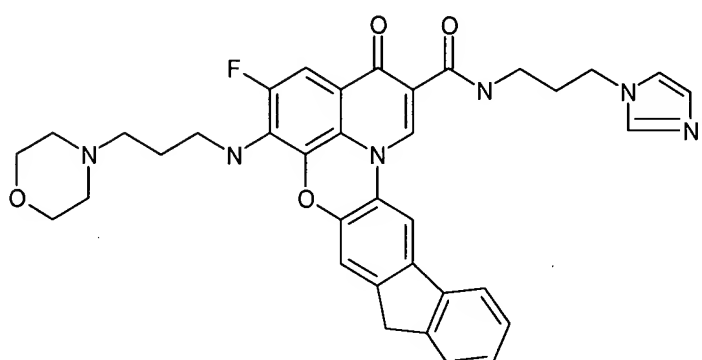
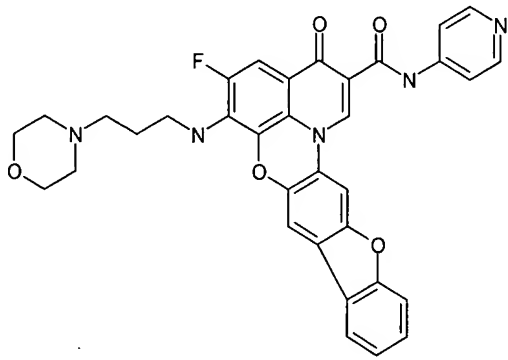
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
301		1.75	
302		1.75	
303		1.5	2.10

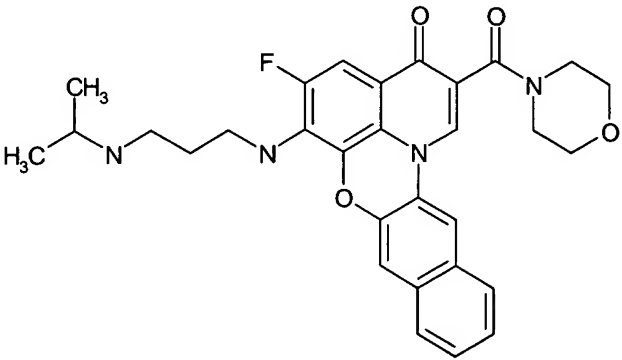
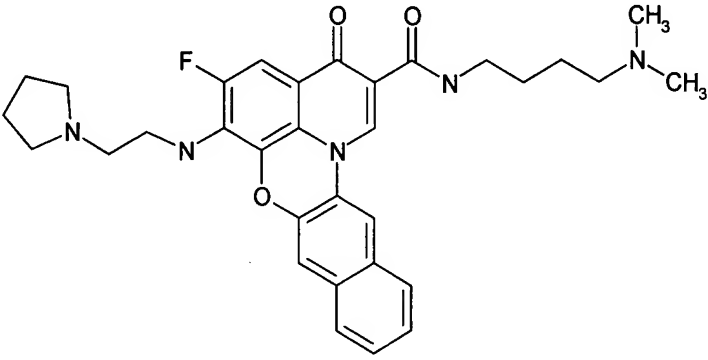
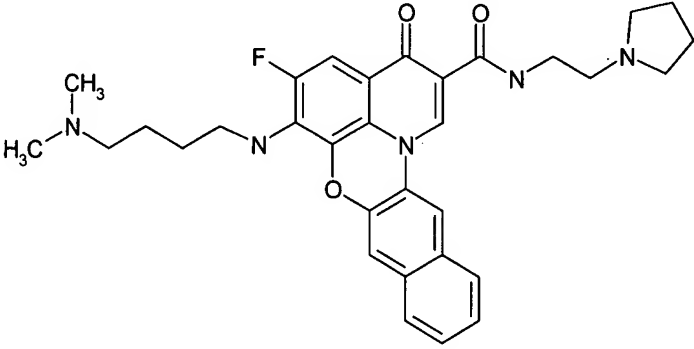
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
304		1.13	
305		1.05	
306		1	3.20



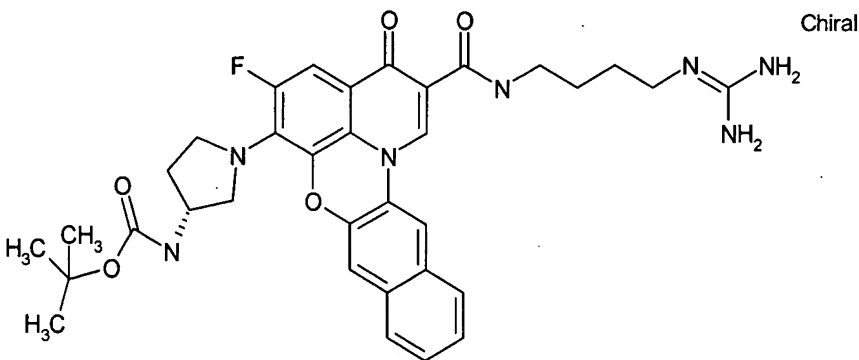
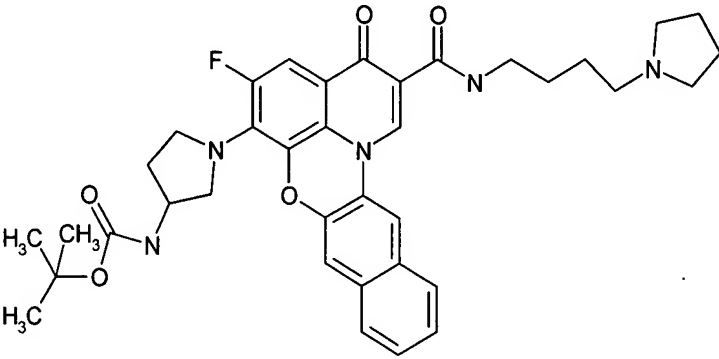
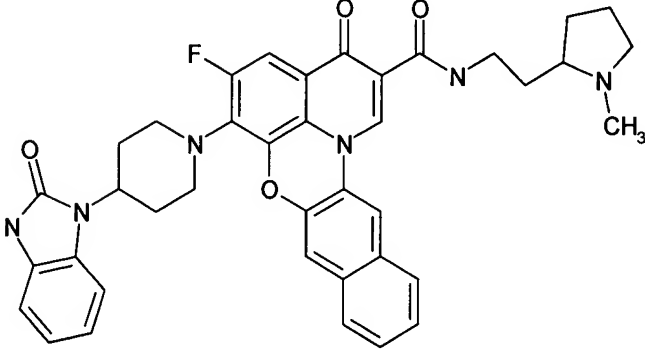
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
307		1	3.10
308		1	3.10
309		1	3.00

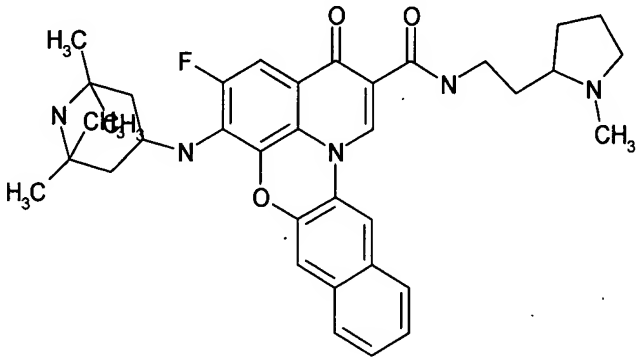
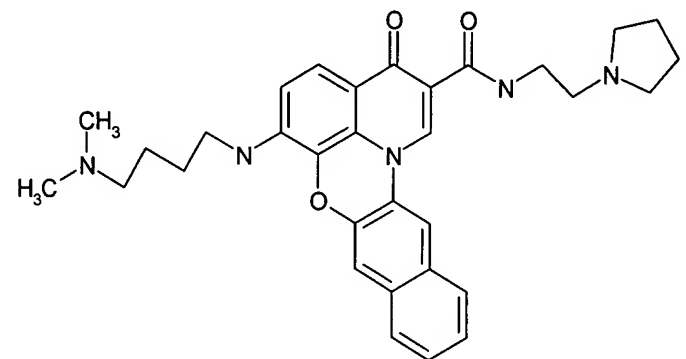
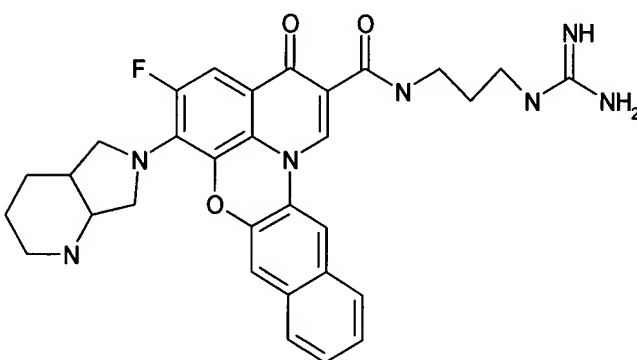
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
310		1	2.30
311		1	2.10
312		1	1.90

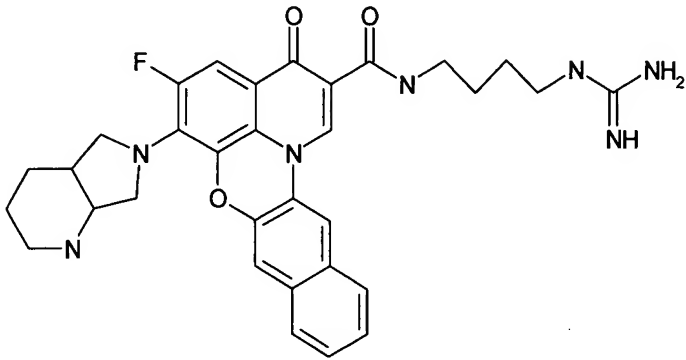
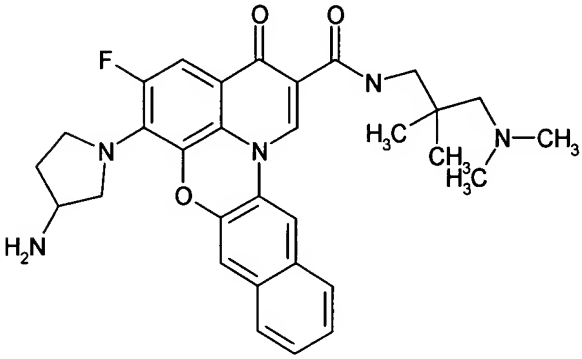
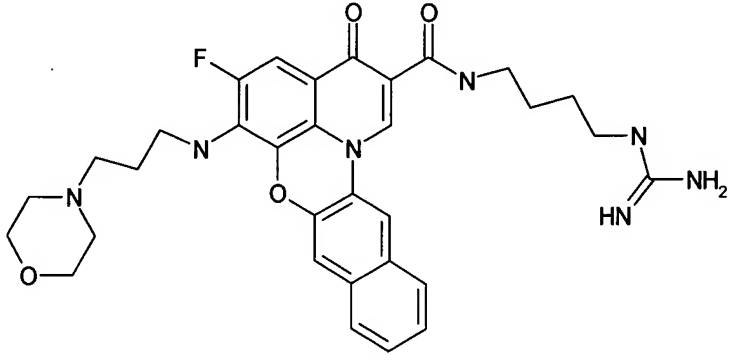
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
313		1	
314		1	
315		1	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
316		1	
317		1	
318		1	

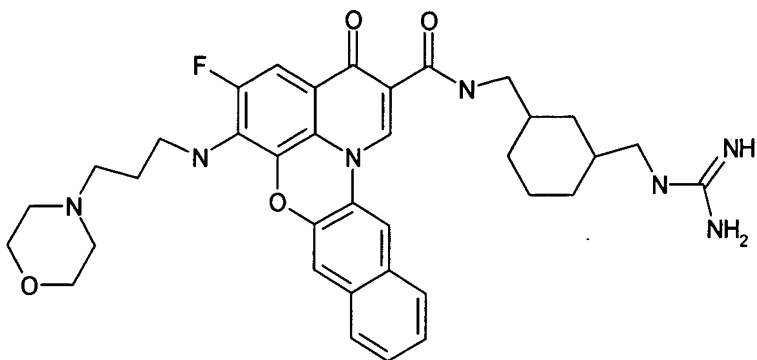
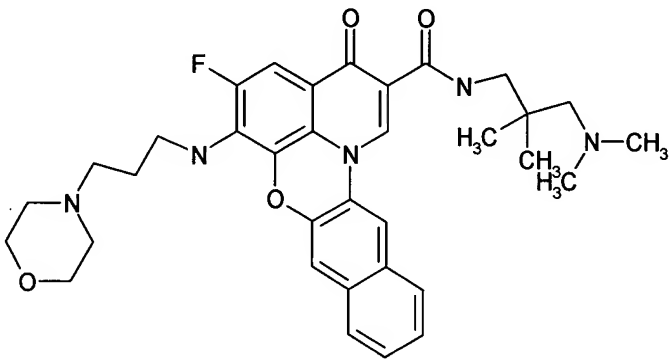
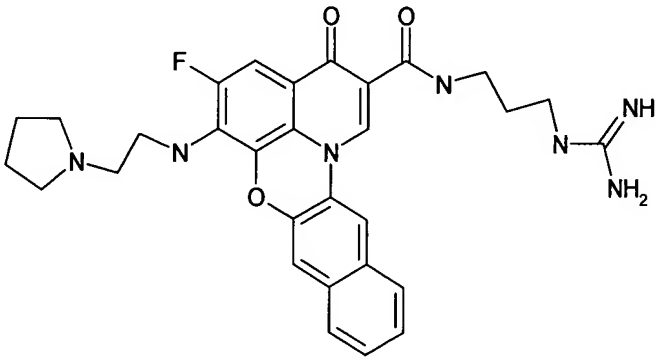
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
319		1	
320		1	
321		1	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
322	 <p style="text-align: right;">Chiral</p>	1	
323		1	
324		1	

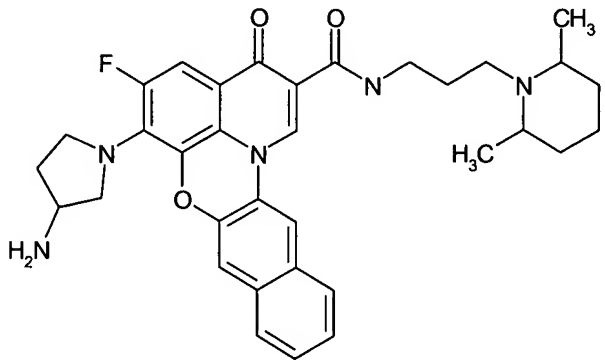
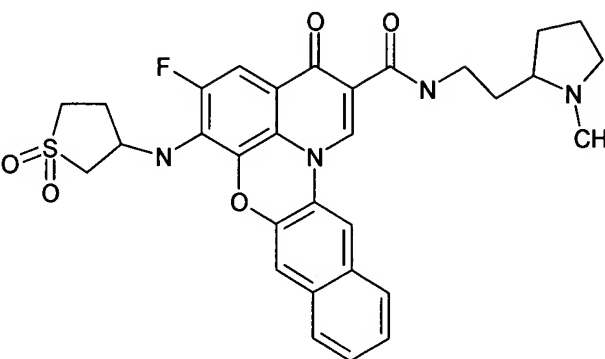
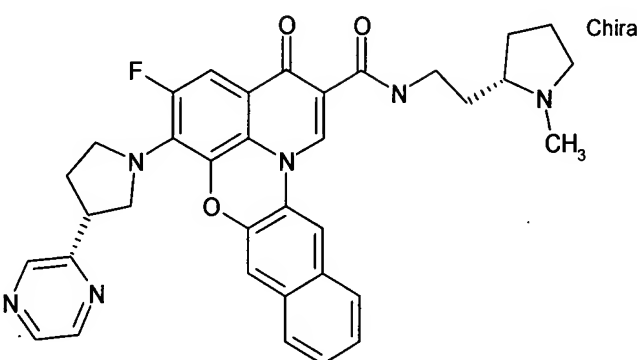
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
325		1	
326		1	
327		1	

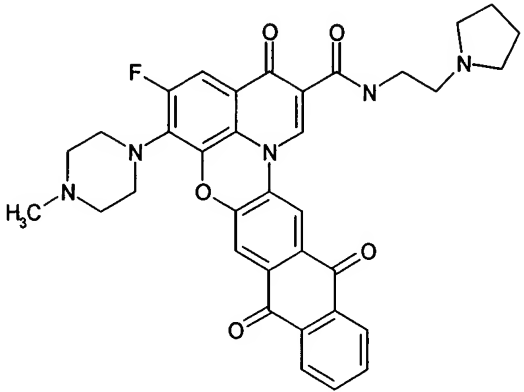
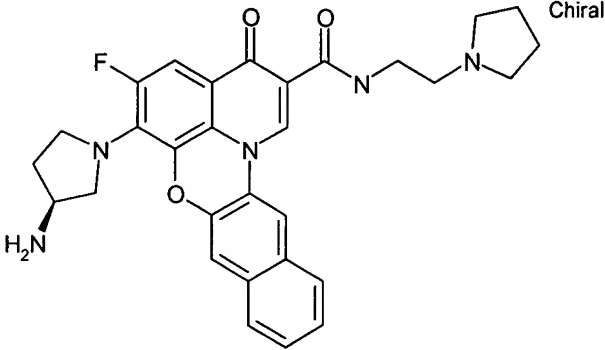
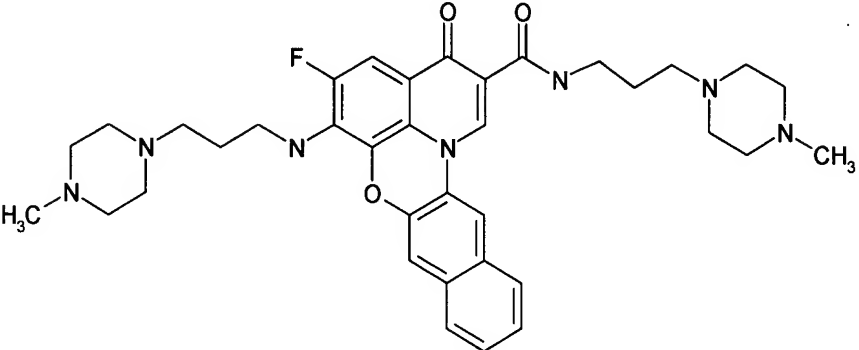
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
328		1	
329		1	
330		1	

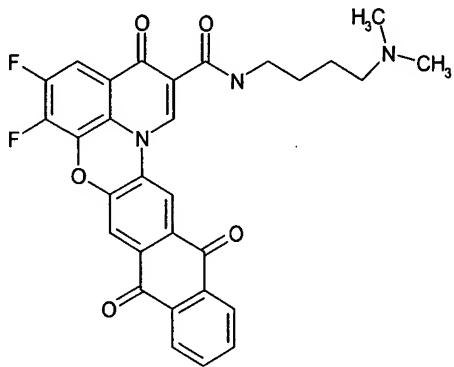
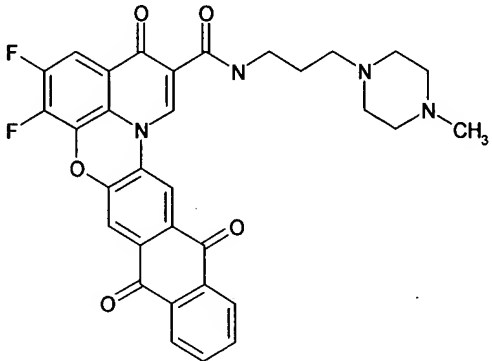
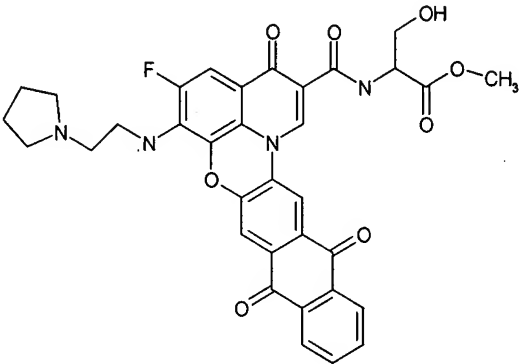


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
331		1	
332		1	
333		1	

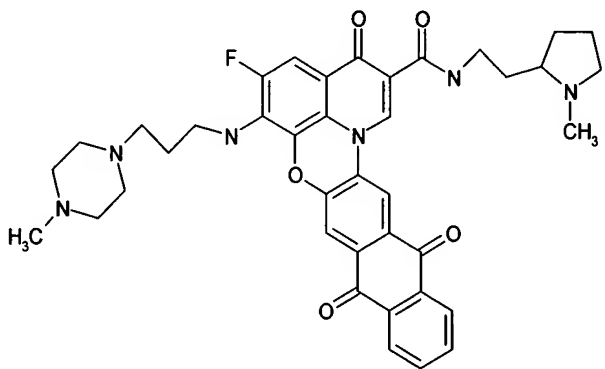
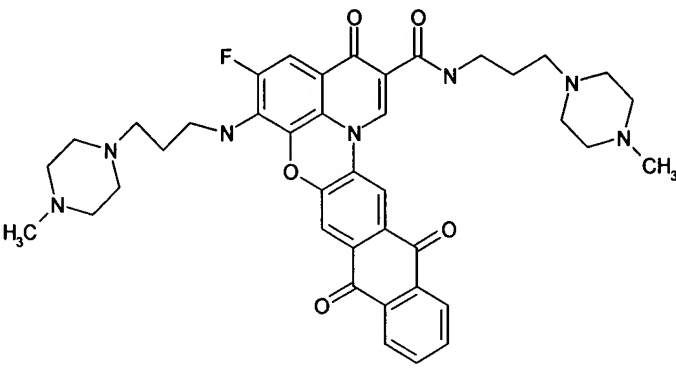
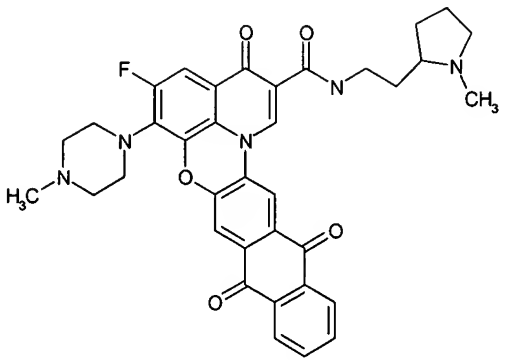
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
334		1	
335		1	
336		1	

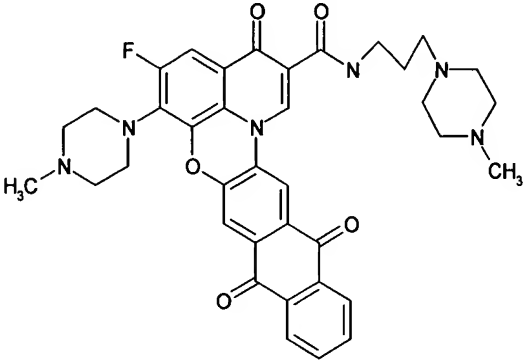
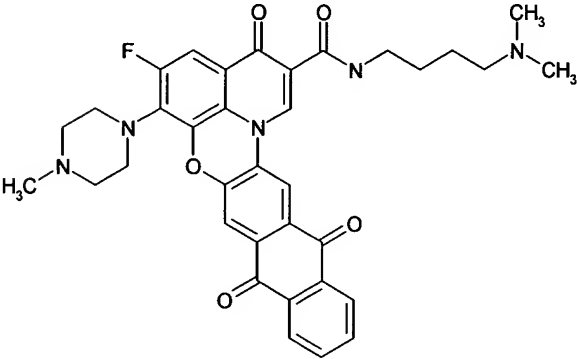
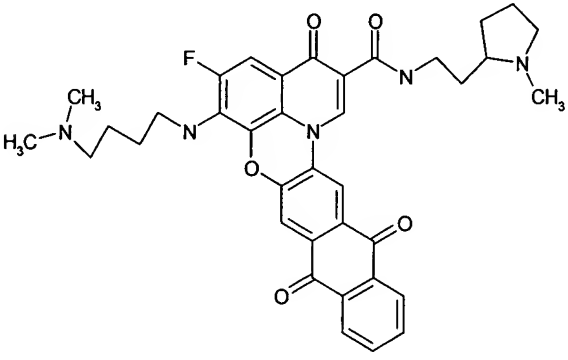
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
337		1	
338		1	
339		0.94	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
340		0.9	8.50
341		0.9	0.28
342		0.9	

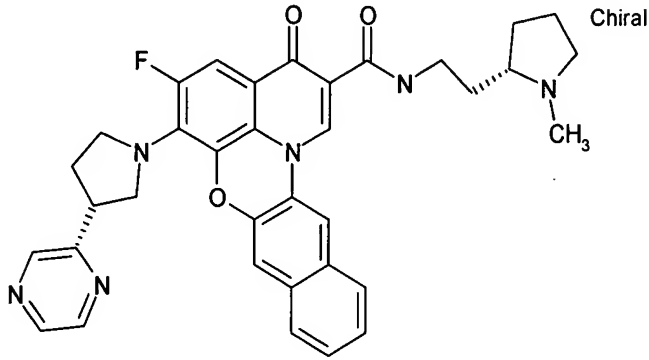
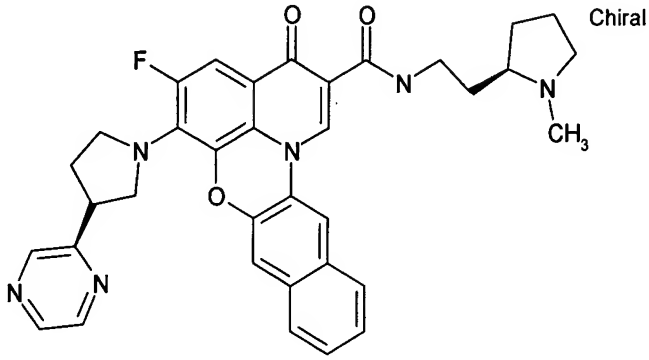
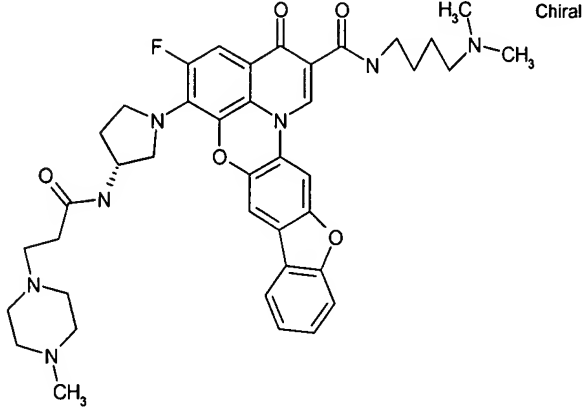
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
343		0.9	
344		0.9	
345		0.9	

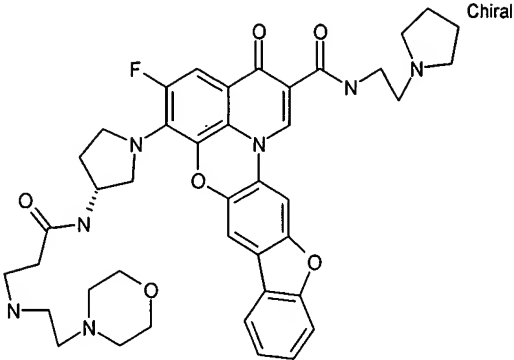
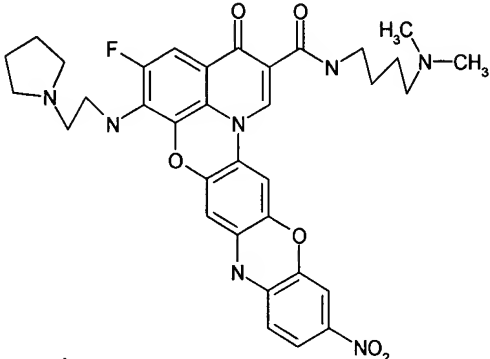
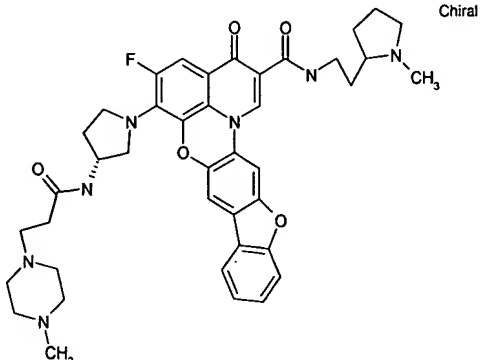
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
346		0.9	
347		0.9	
348		0.9	

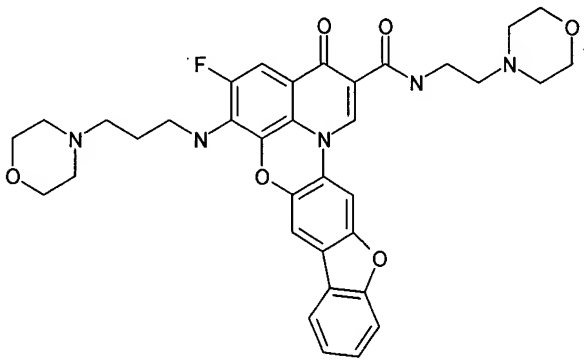
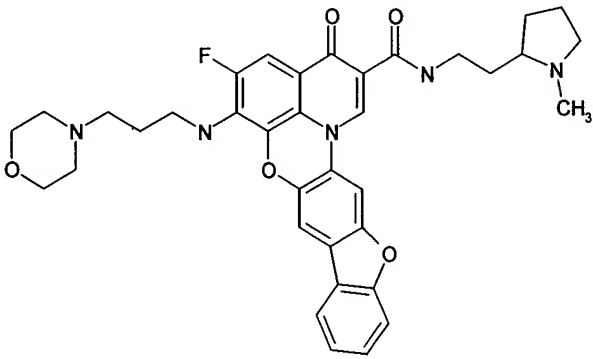
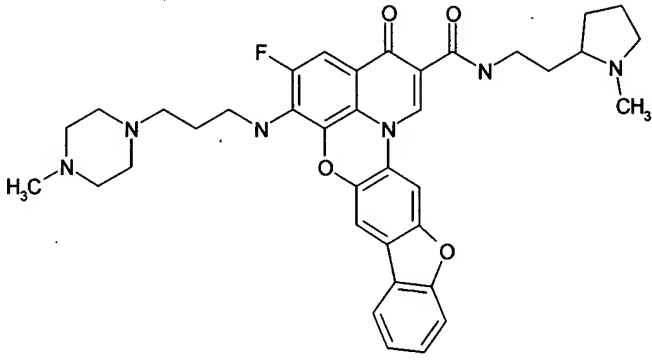
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
349		0.9	
350		0.9	
351		0.9	

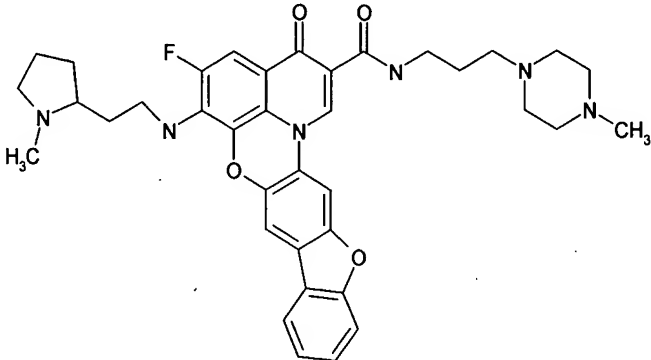
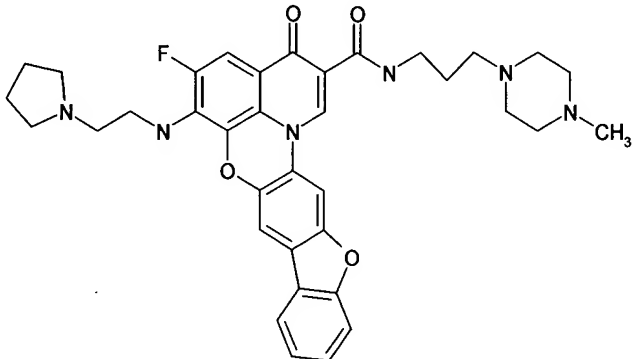
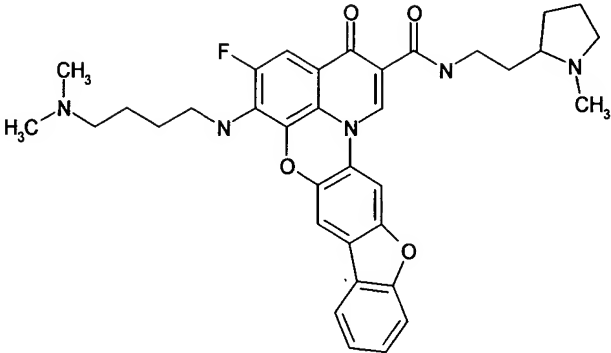
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
352		0.9	
353		0.9	
354		0.9	

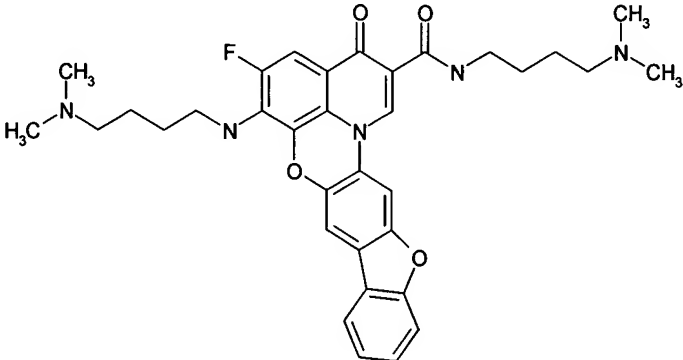
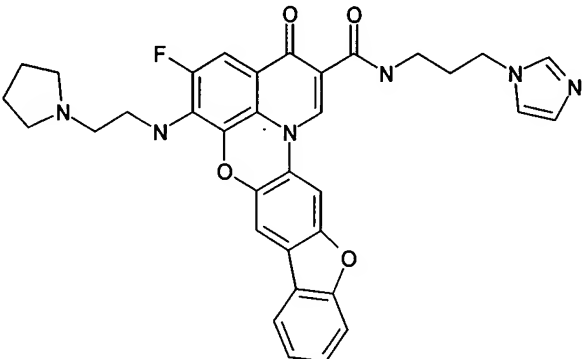
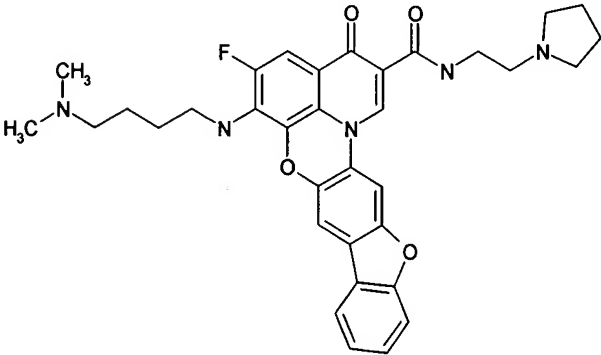


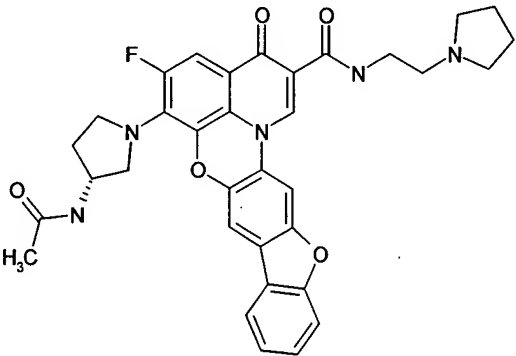
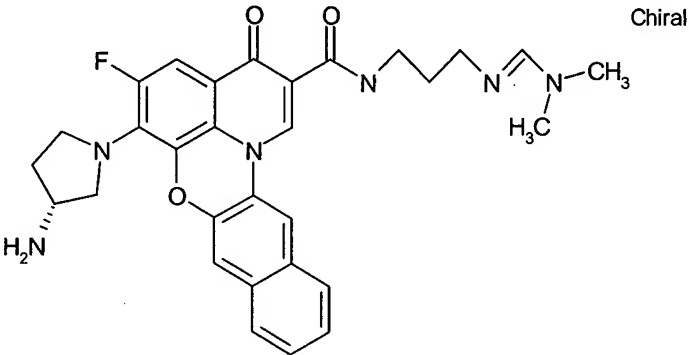
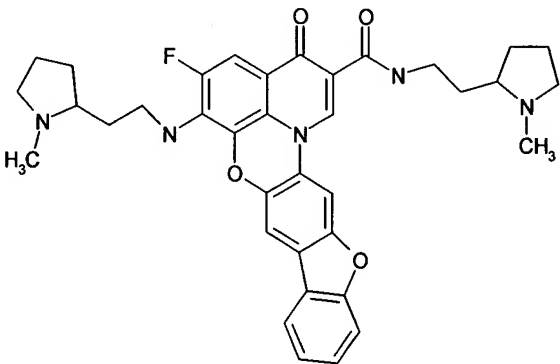
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
355		0.89	
356		0.85	
357		0.75	8.60

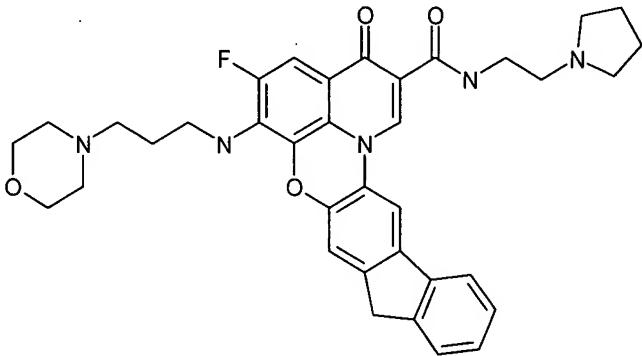
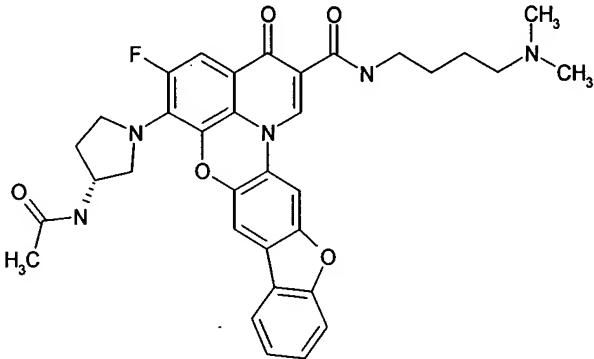
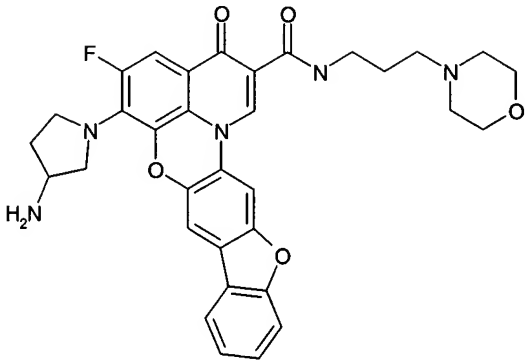
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
358		0.75	5.70
359		0.75	4.80
360		0.75	4.50

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
361		0.75	4.20
362		0.75	4.00
363		0.75	3.80

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
364		0.75	3.80
365		0.75	3.80
366		0.75	3.70

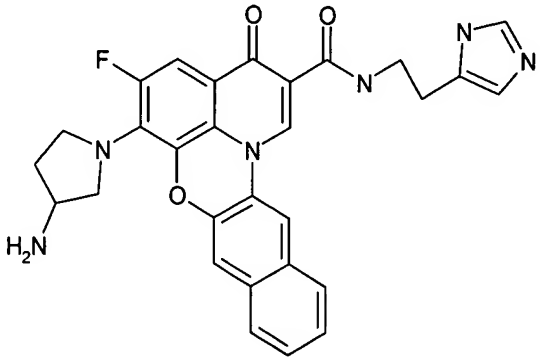
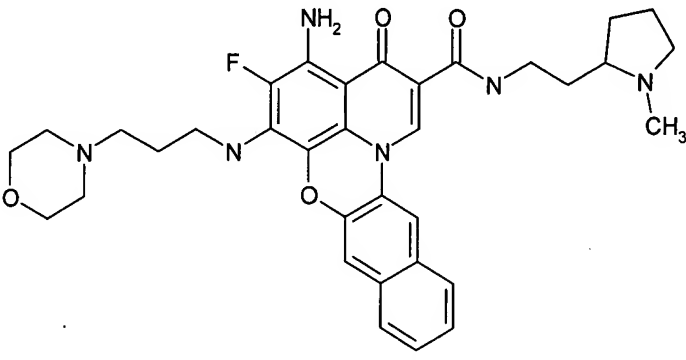
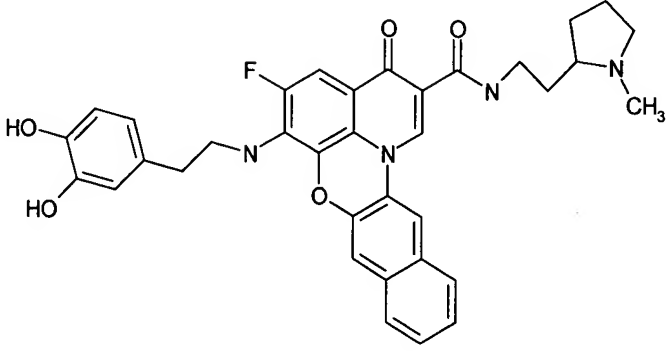
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
367		0.75	3.70
368		0.75	3.60
369		0.75	3.50

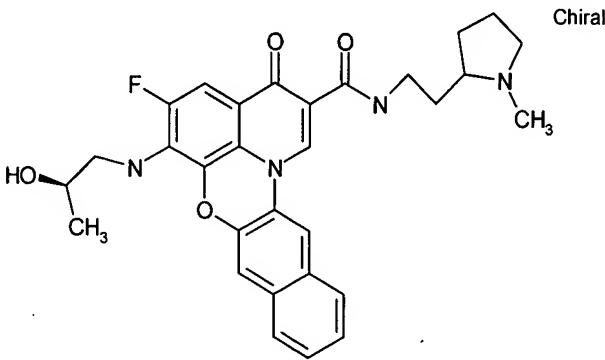
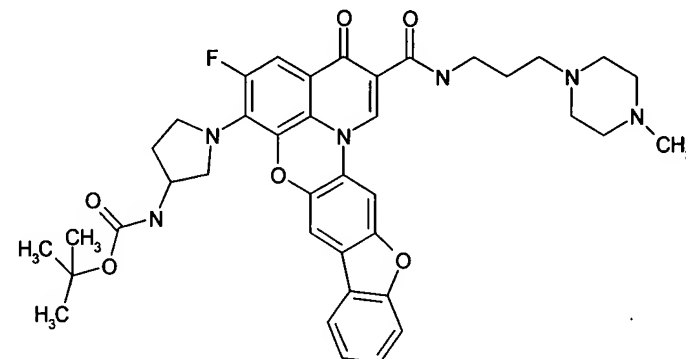
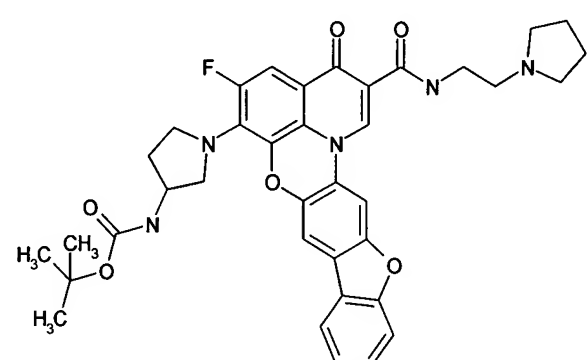
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
370		0.75	3.50
371		0.75	3.50
372		0.75	3.40

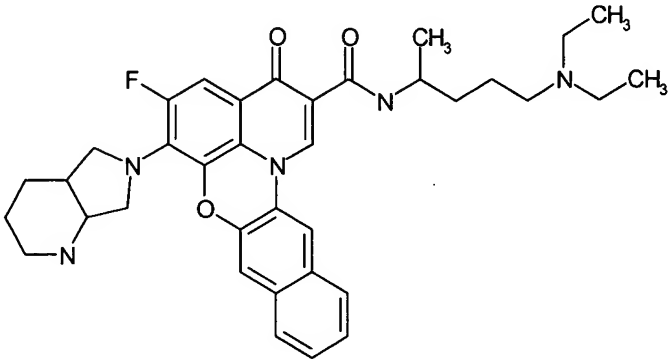
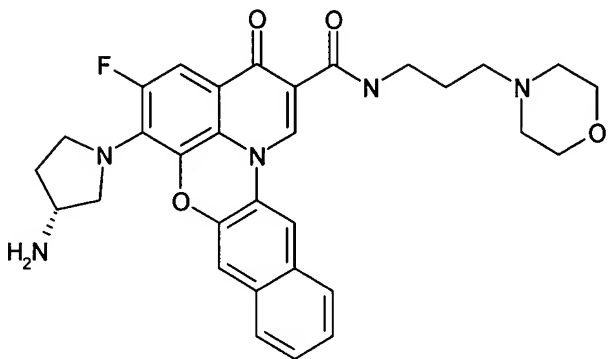
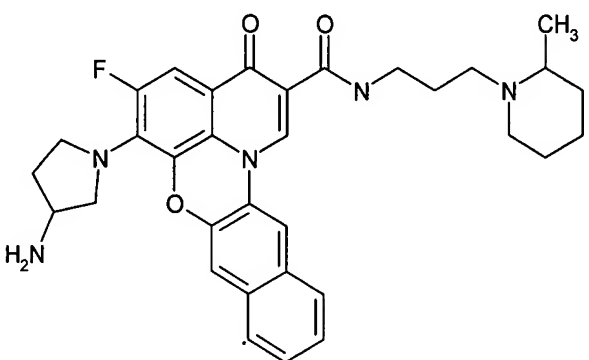
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
373		0.75	3.30
374		0.75	3.30
375		0.75	2.70

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
376		0.75	2.40
377		0.75	2.20
378		0.75	2.10



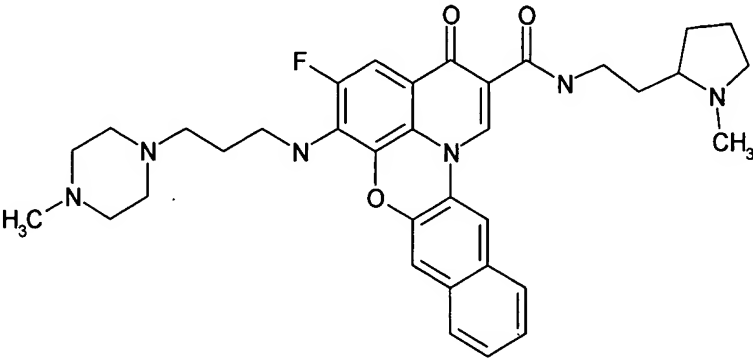
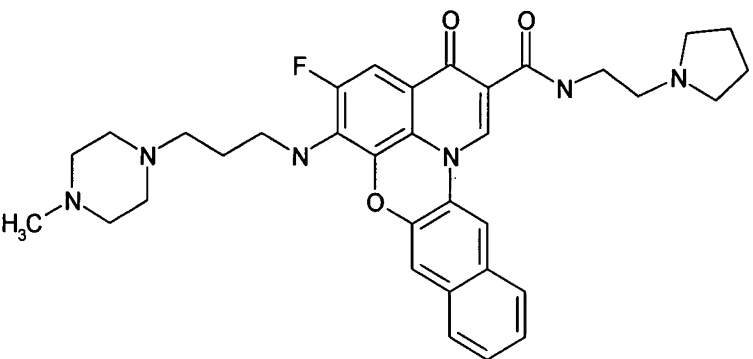
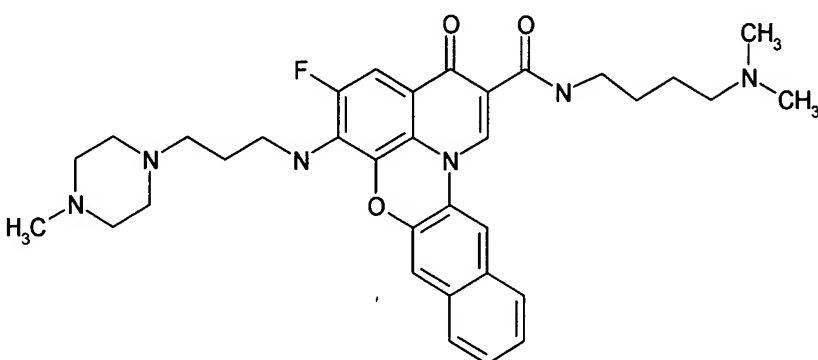
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
379		0.75	1.90
380		0.75	1.80
381		0.75	1.80

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
382	 <p>Chiral</p>	0.75	1.80
383		0.75	0.37
384		0.75	0.37

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
385		0.75	0.36
386		0.75	0.34
387		0.75	0.33

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
388		0.75	0.31
389		0.75	0.29
390		0.75	0.24

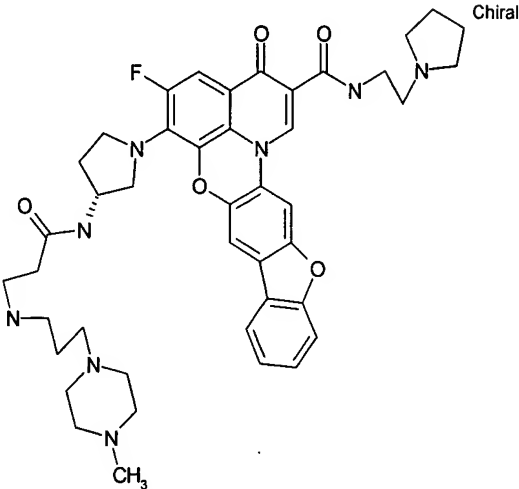
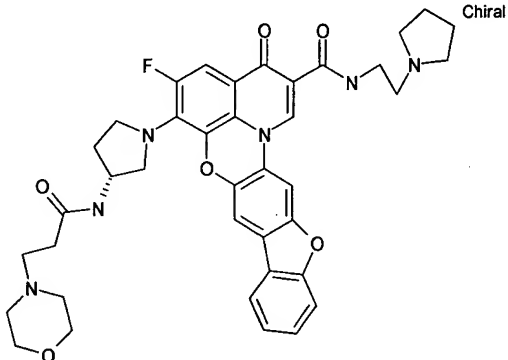
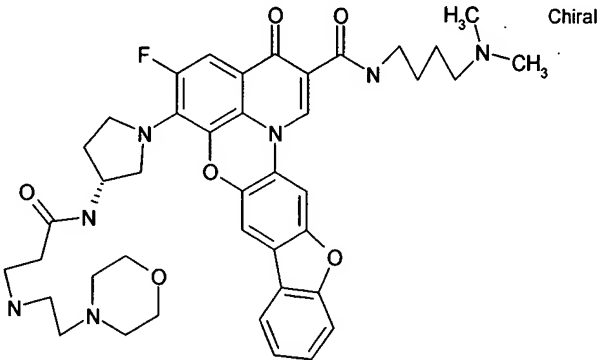
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
391		0.75	0.24
392		0.75	0.19
393		0.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
394		0.75	
395		0.75	
396		0.75	

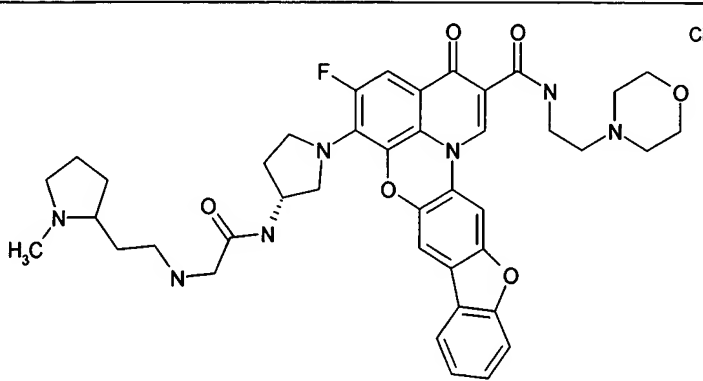
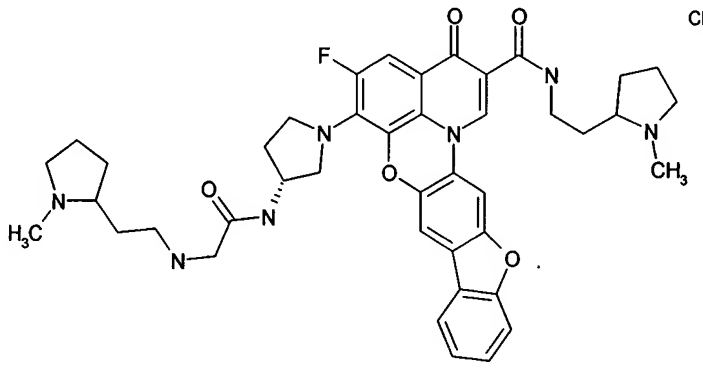
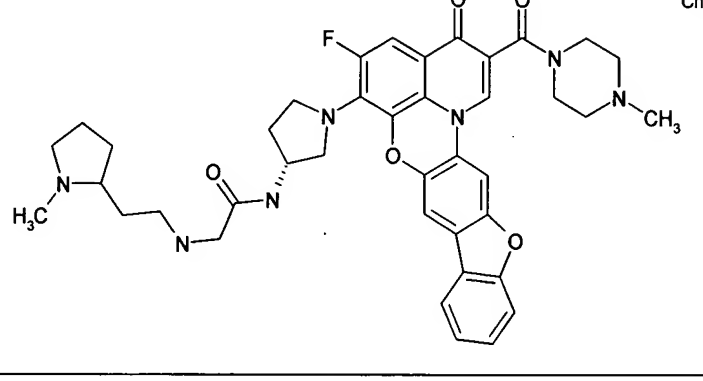
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
397		0.75	
398		0.75	
399		0.75	

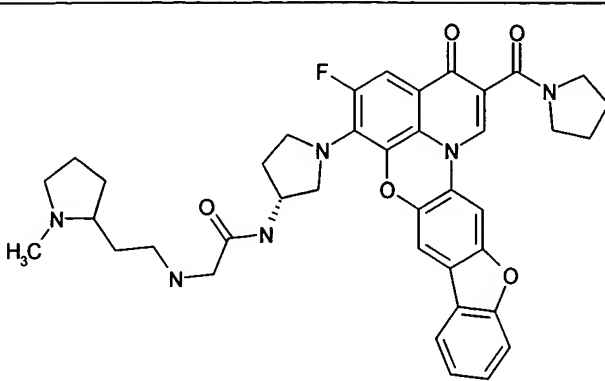
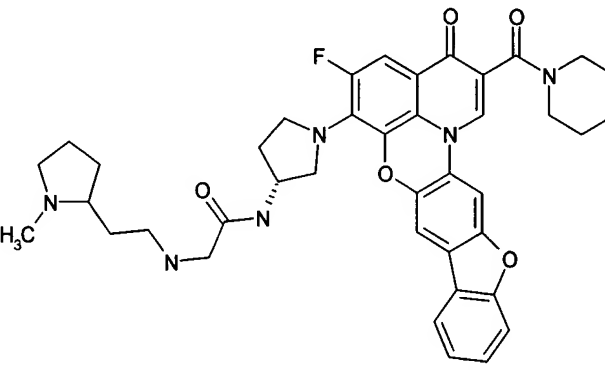
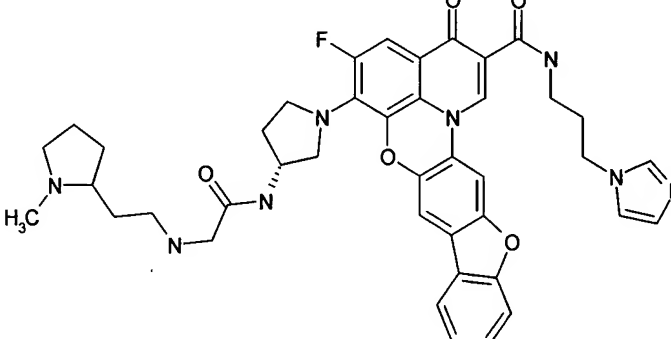
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
400		0.75	
401		0.75	
402		0.75	

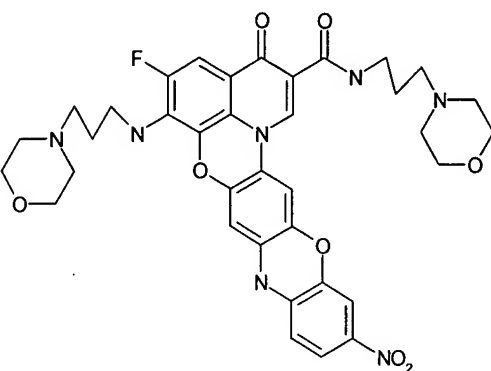
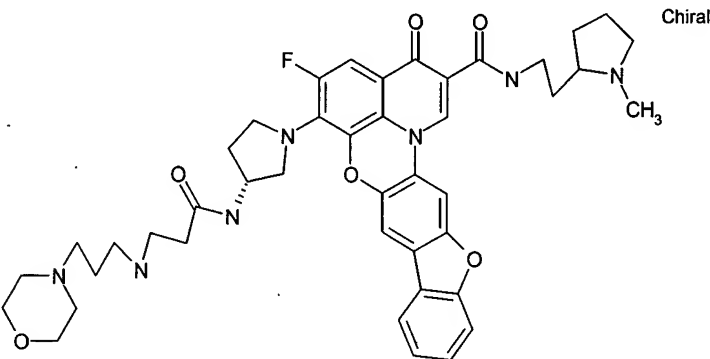
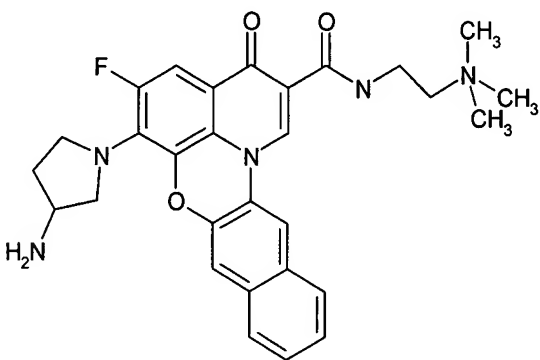


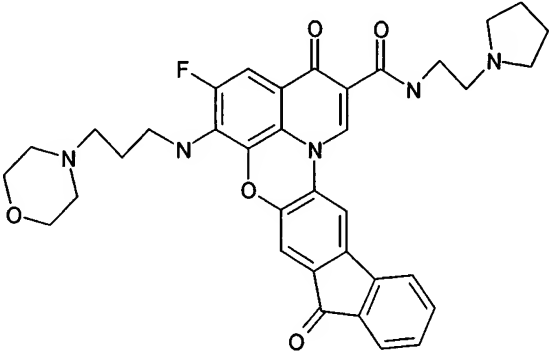
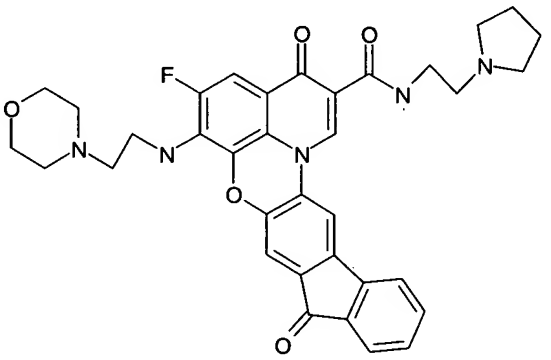
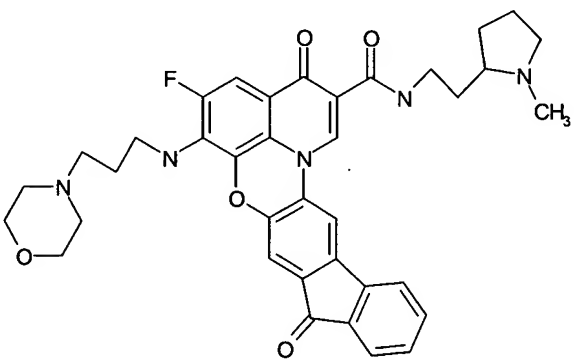
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
403	 <p>Chiral</p>	0.75	
404	 <p>Chiral</p>	0.75	
405	 <p>Chiral</p>	0.75	

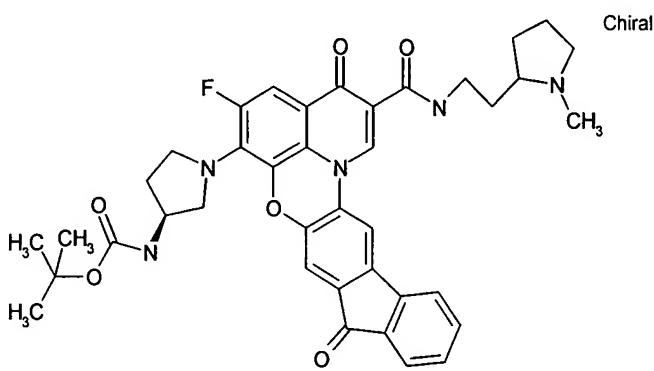
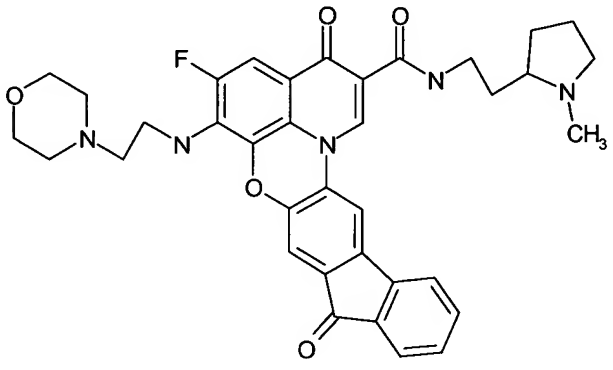
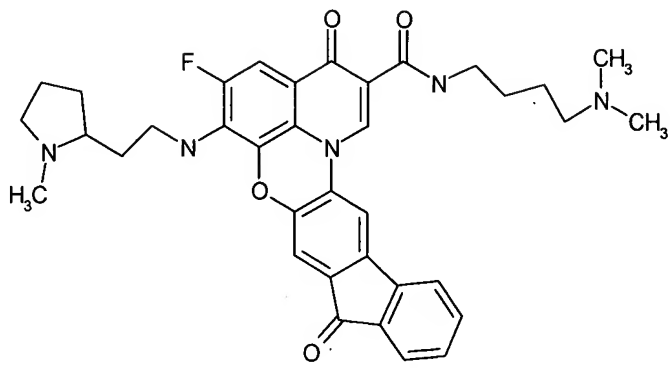
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
406		0.75	
407		0.75	
408		0.75	

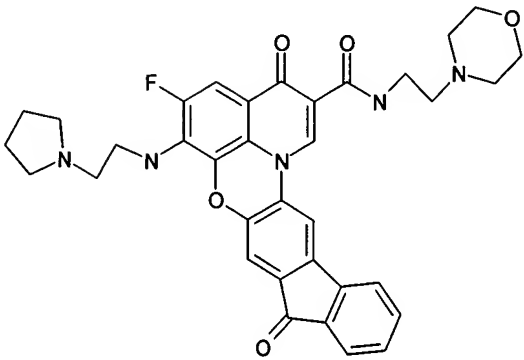
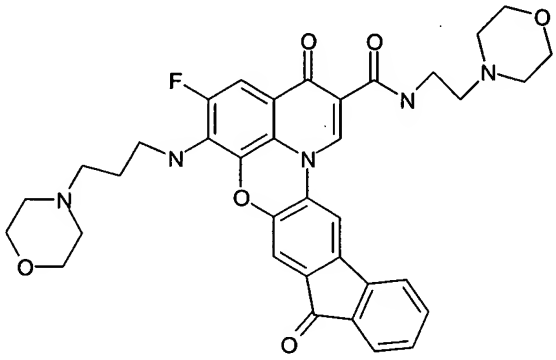
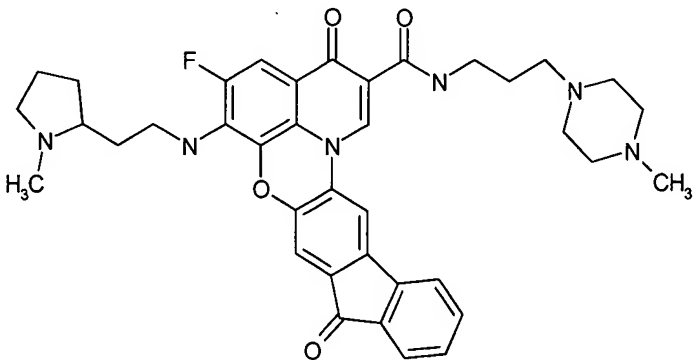
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
409		0.75	
410		0.75	
411		0.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
412	<p>Chiral</p> 	0.75	
413	<p>Chiral</p> 	0.75	
414	<p>Chiral</p> 	0.75	

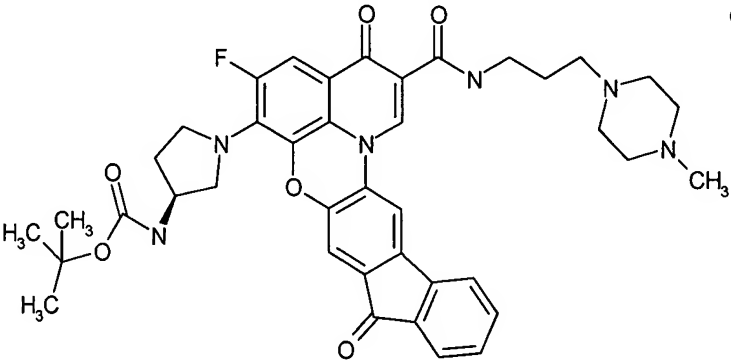
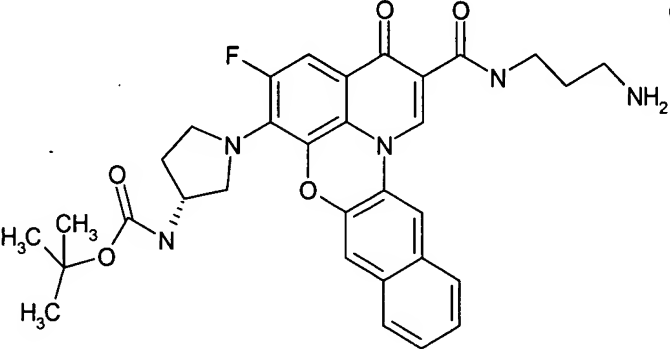
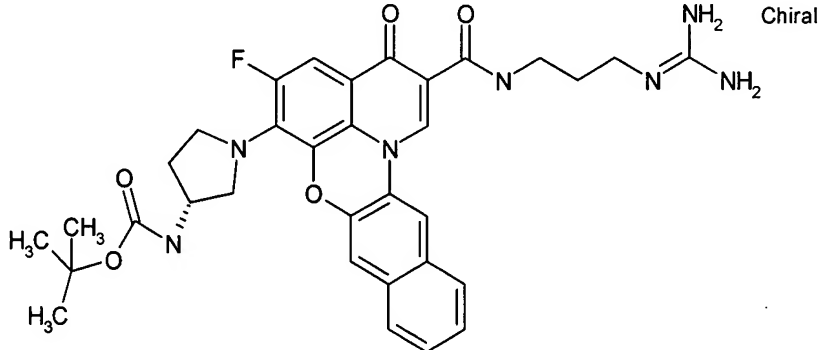
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
415		0.75	
416		0.75	
417		0.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
418		0.75	
419		0.75	
420		0.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
421	 <p>Chiral</p>	0.75	
422		0.75	
423		0.75	

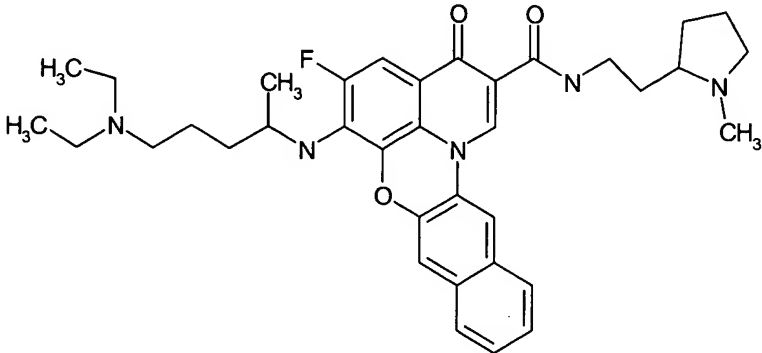
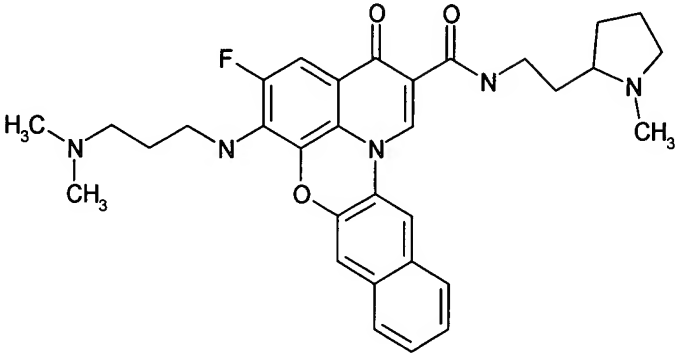
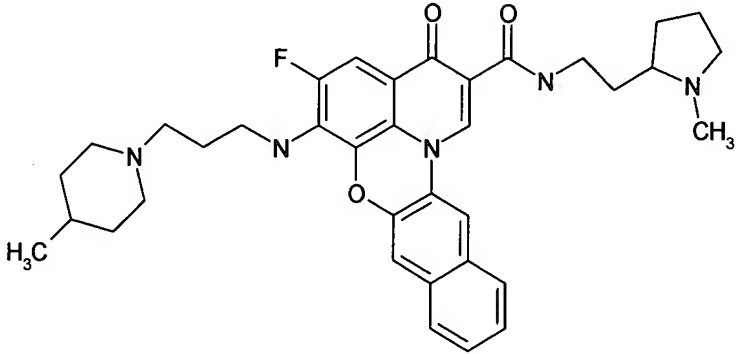
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
424		0.75	
425		0.75	
426		0.75	

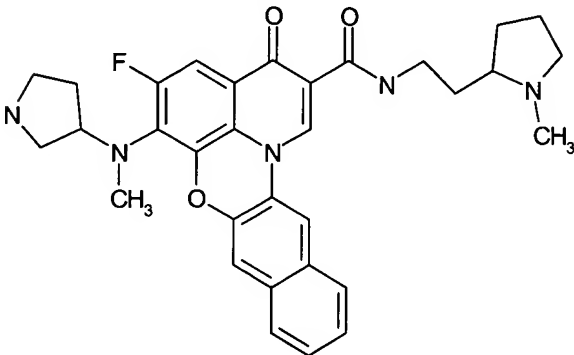
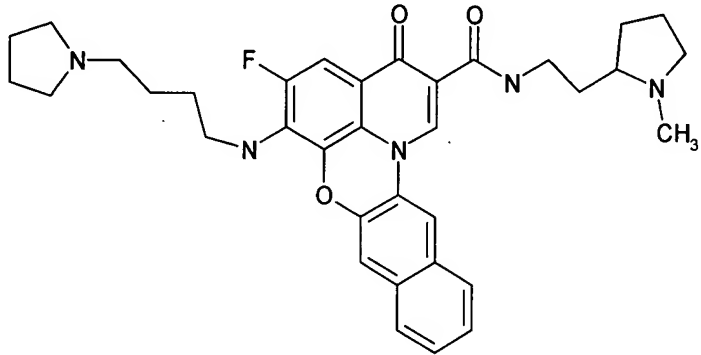
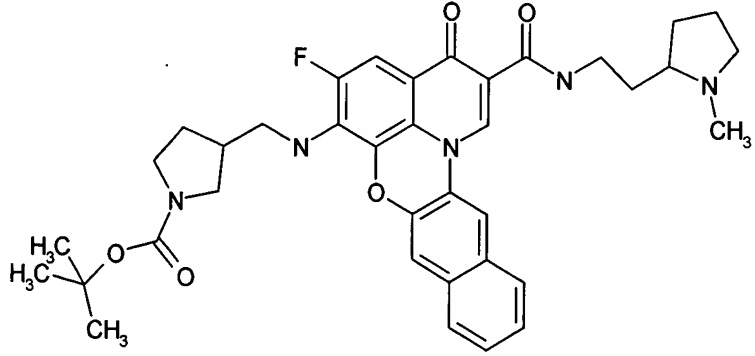


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
427	<div style="display: flex; align-items: center; justify-content: space-between;">  <span>Chiral</span> </div>	0.75	
428	<div style="display: flex; align-items: center; justify-content: space-between;">  <span>Chiral</span> </div>	0.75	
429	<div style="display: flex; align-items: center; justify-content: space-between;">  <span>Chiral</span> </div>	0.75	

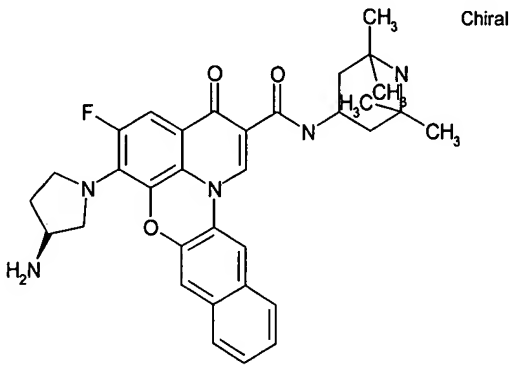
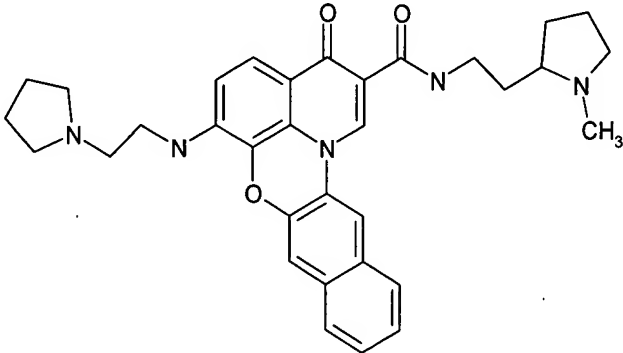
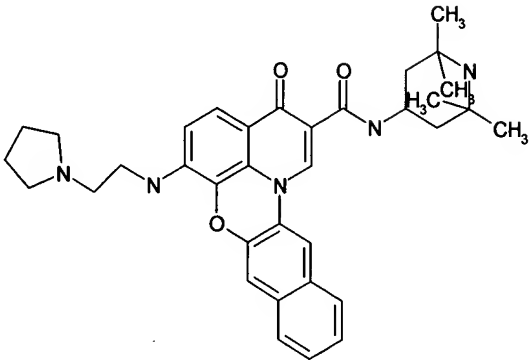
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
430		0.75	
431		0.75	
432		0.75	

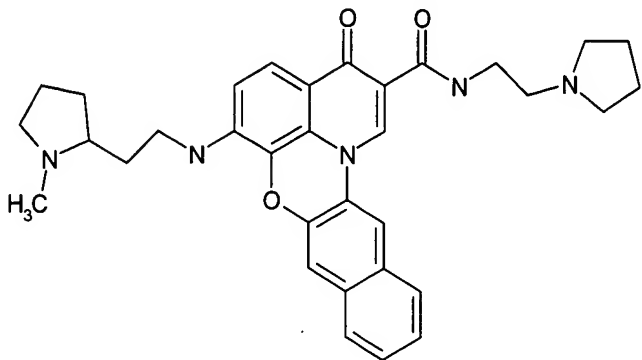
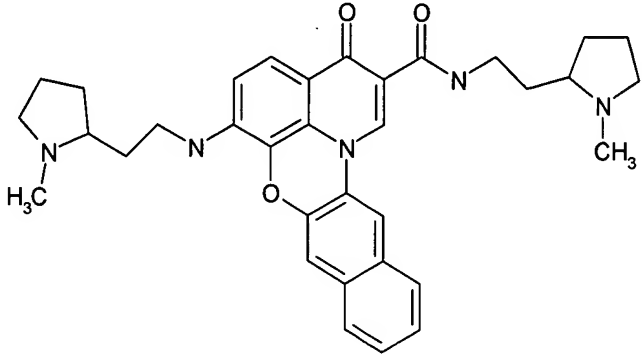
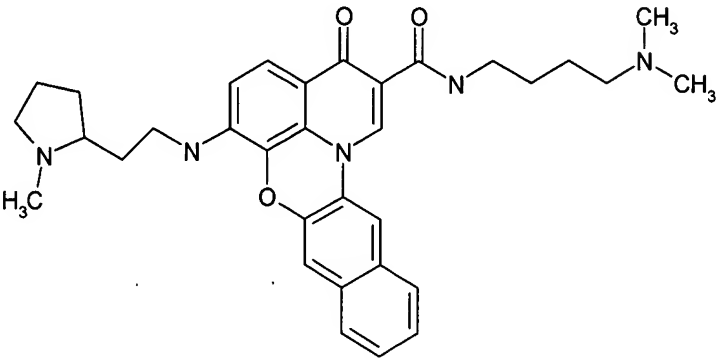
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
433		0.75	
434		0.75	
435		0.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
436		0.75	
437		0.75	
438		0.75	

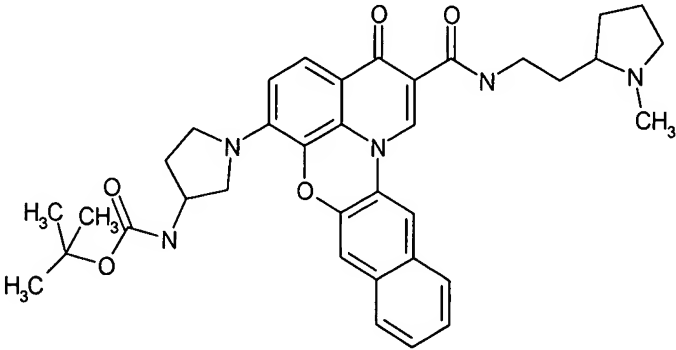
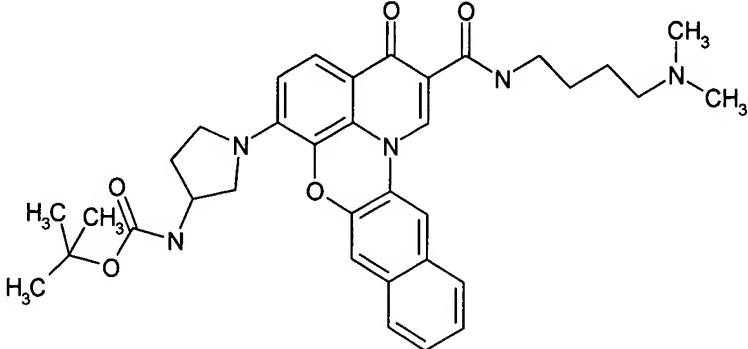
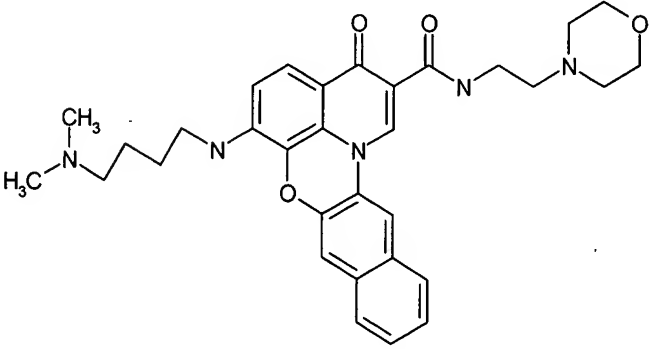
	Structure	Stop Data c-Myc $\mu\text{M}$	MTS Data Hella $\mu\text{M}$
439		0.75	
440		0.75	
441		0.75	

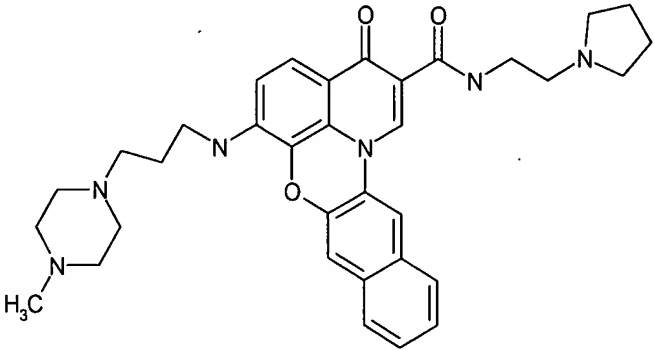
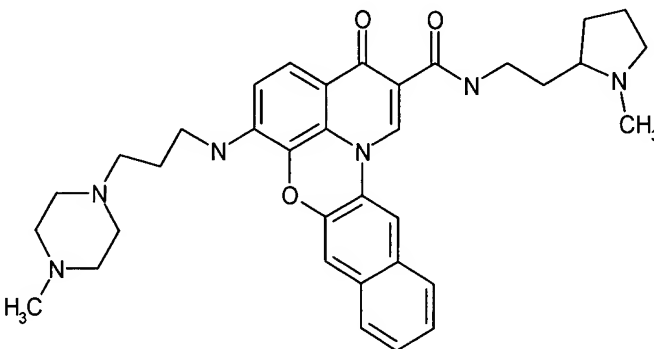
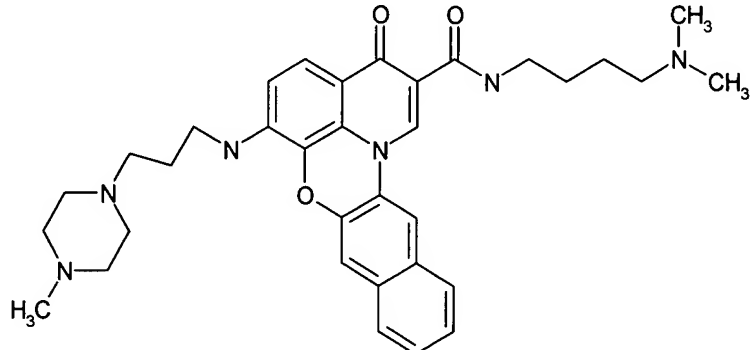
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
442		0.75	
443		0.75	
444		0.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
445		0.75	
446		0.75	
447		0.75	

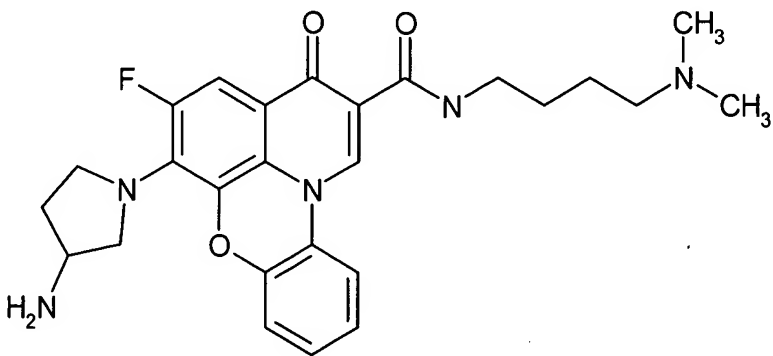
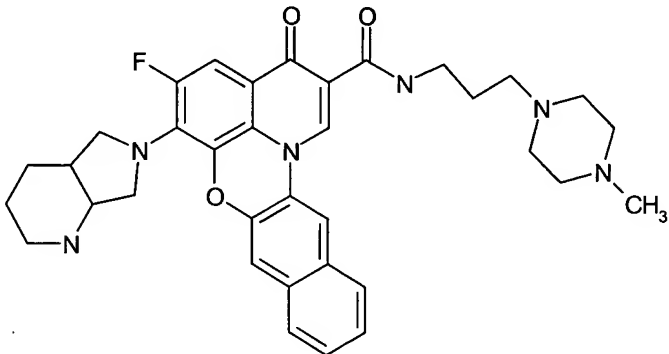
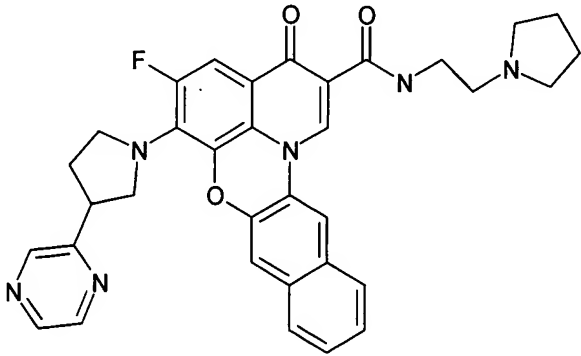
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
448		0.75	
449		0.75	
450		0.75	

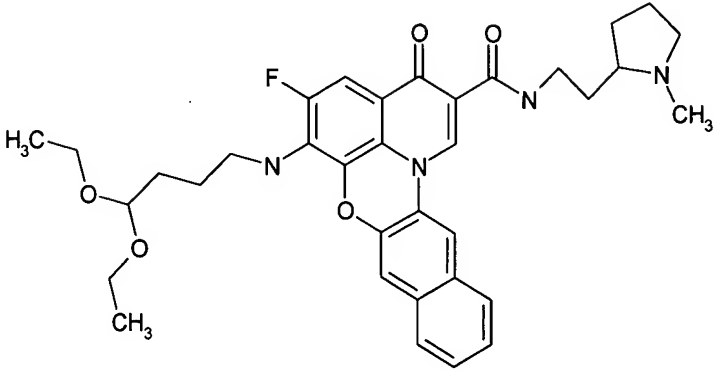
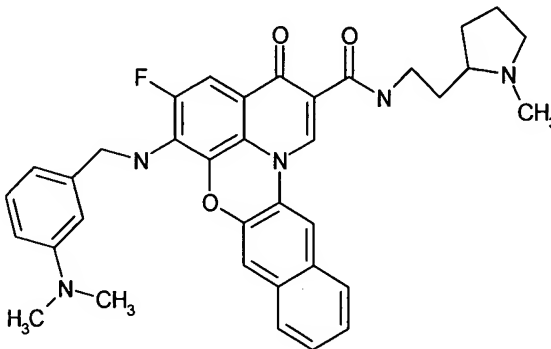
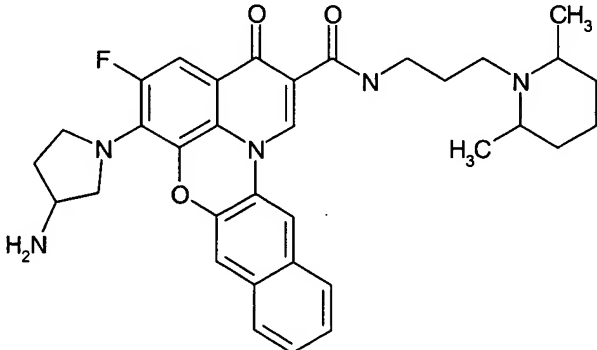


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
451		0.75	
452		0.75	
453		0.75	

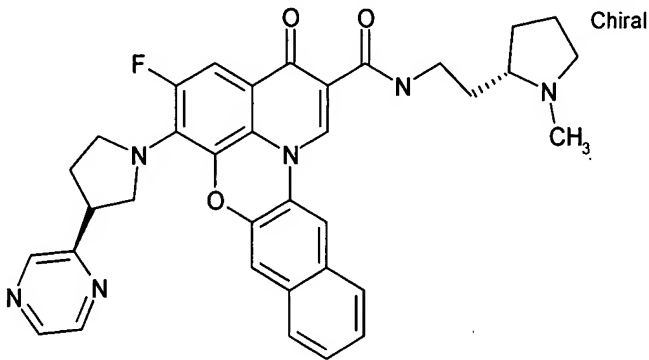
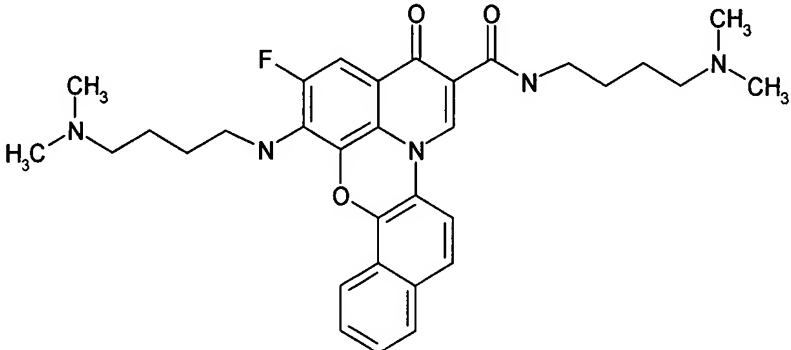
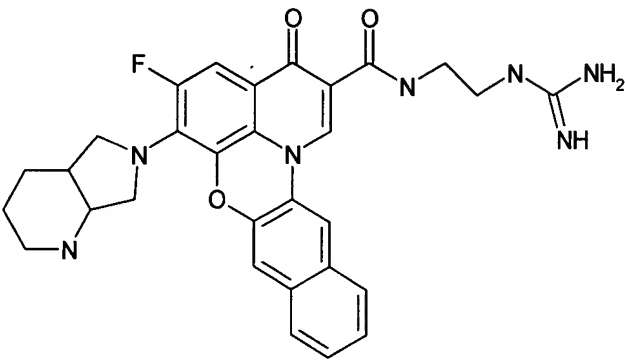
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
454		0.75	
455		0.75	
456		0.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
457		0.75	
458		0.75	
459		0.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
460		0.75	
461		0.75	
462		0.75	

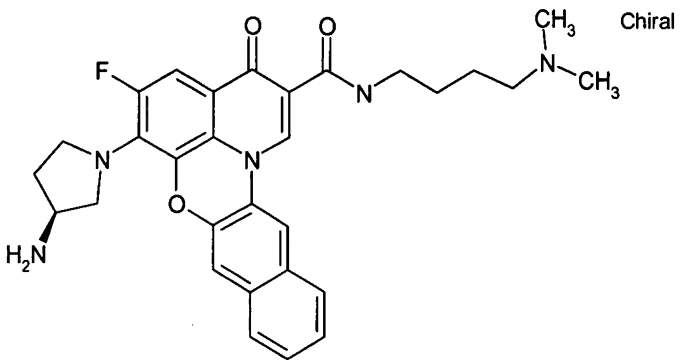
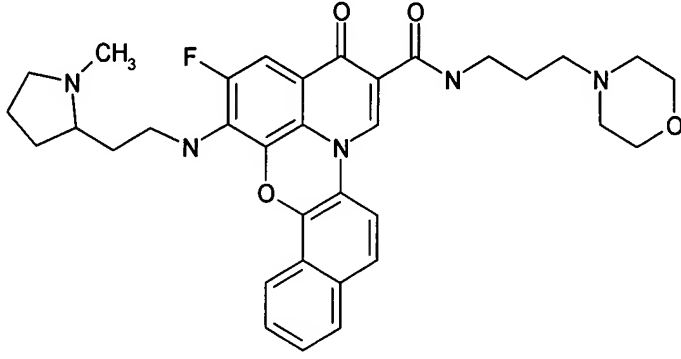
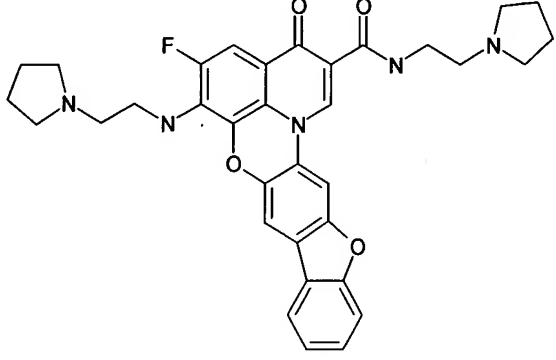
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
463		0.75	
464		0.75	
465		0.75	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
466		0.75	
467		0.75	
468		0.74	

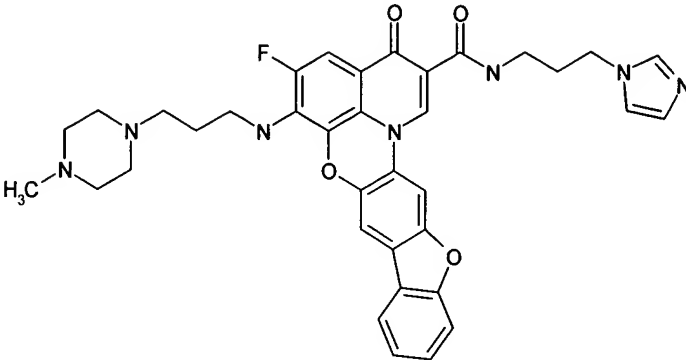
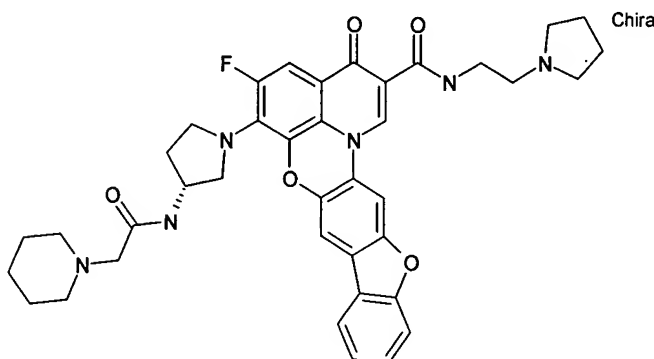
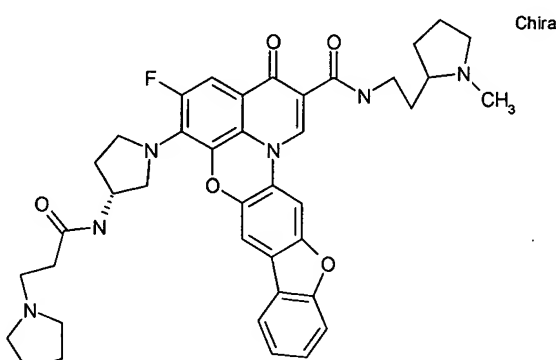
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
469		0.73	
470		0.64	
471		0.64	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
472		0.62	3.30
473		0.62	
474		0.58	0.37

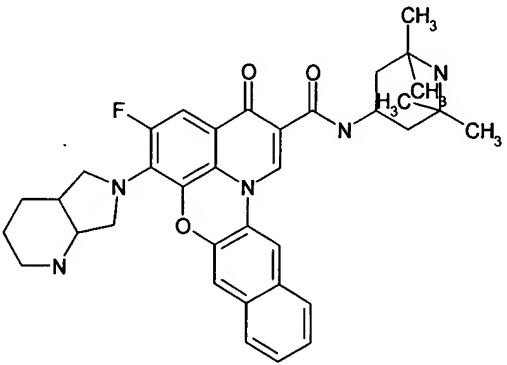
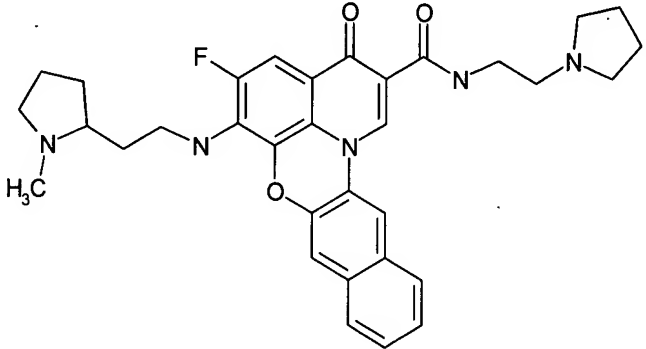
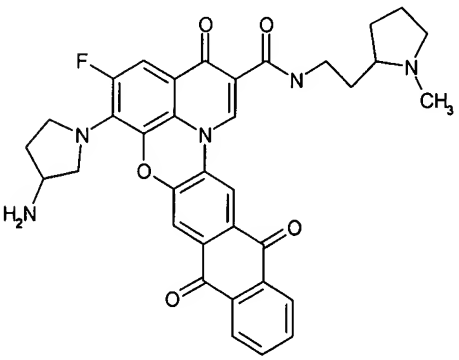


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
475		0.58	0.24
476		0.58	
477		0.55	2.10

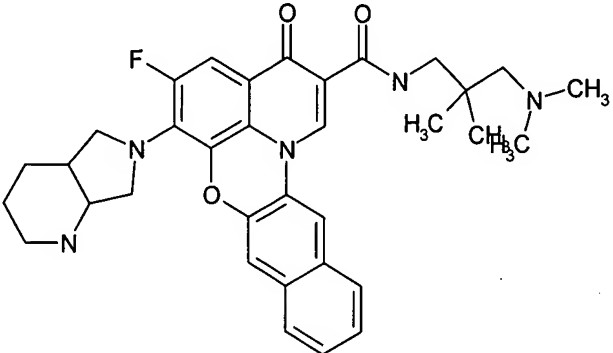
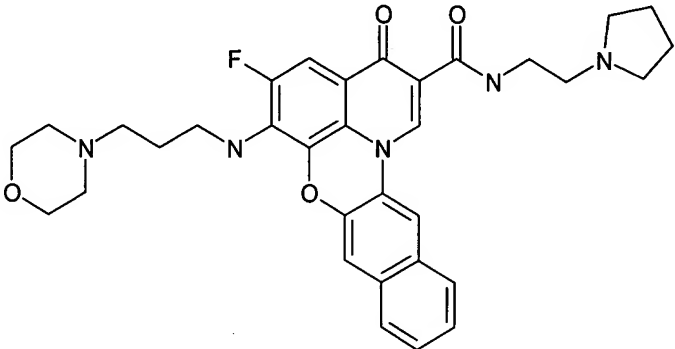
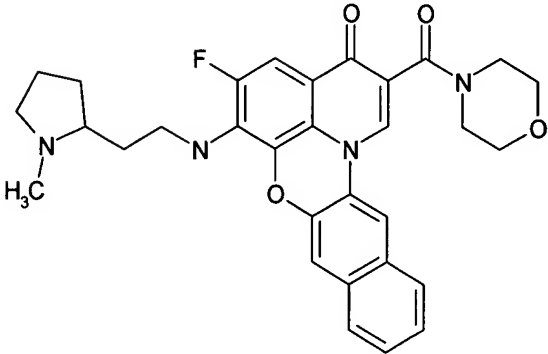
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
478		0.53	
479		0.5	7.40
480		0.5	3.70

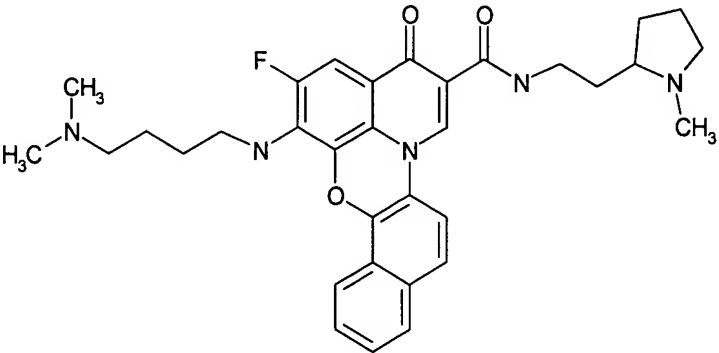
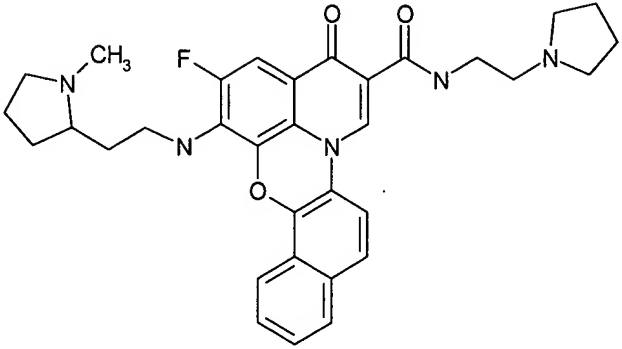
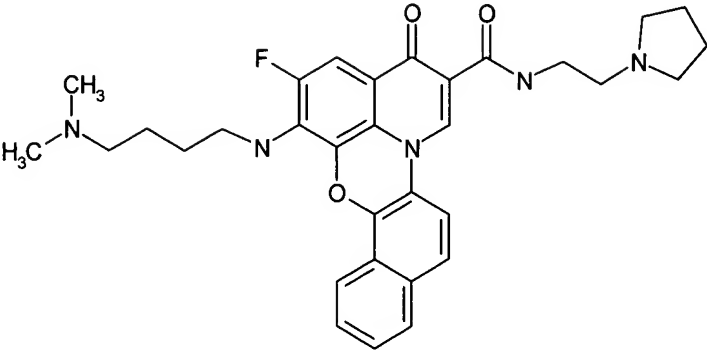
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
481		0.5	3.60
482		0.5	3.40
483		0.5	3.20



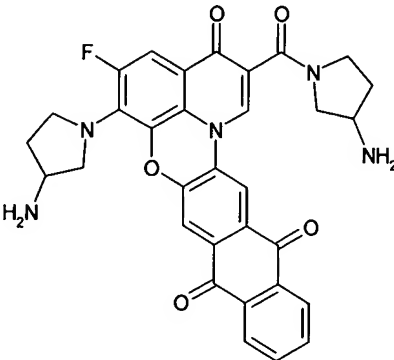
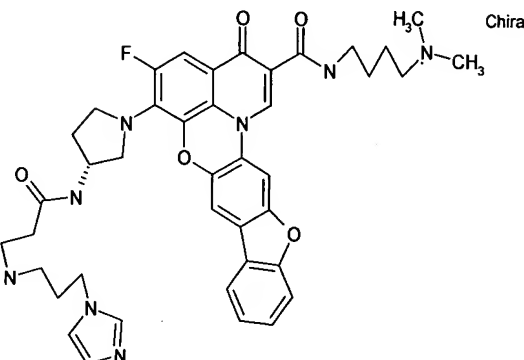
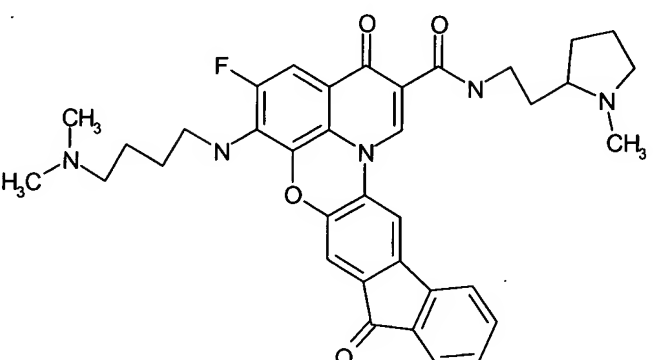
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
487		0.5	0.18
488		0.5	
489		0.5	

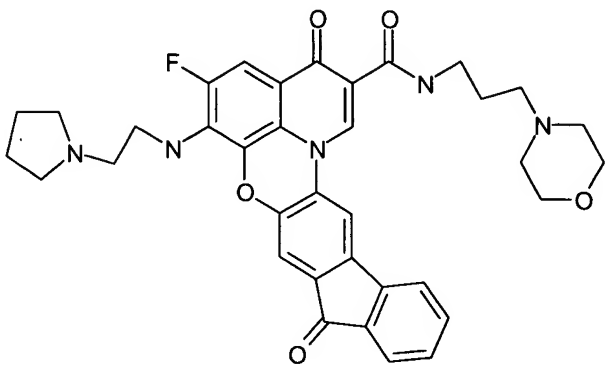
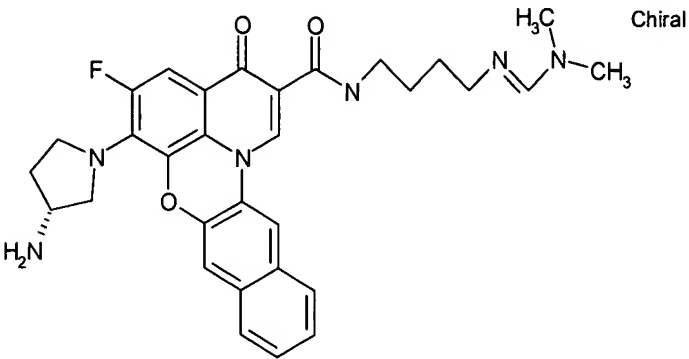
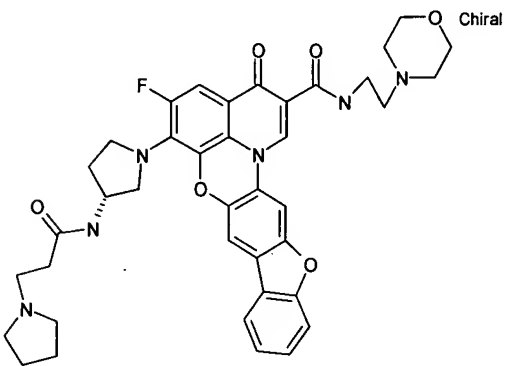
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
490		0.5	
491		0.45	
492		0.45	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
493		0.44	0.40
494		0.44	0.19
495		0.42	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
496		0.41	4.00
497		0.41	2.10
498		0.41	

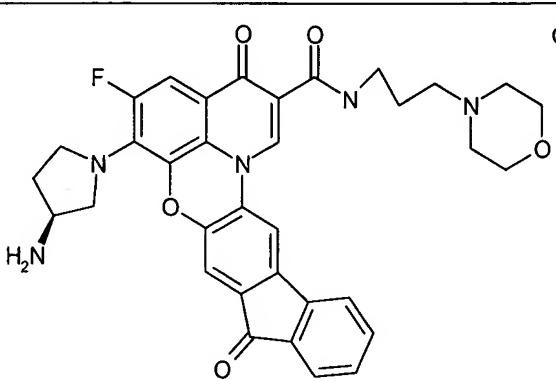
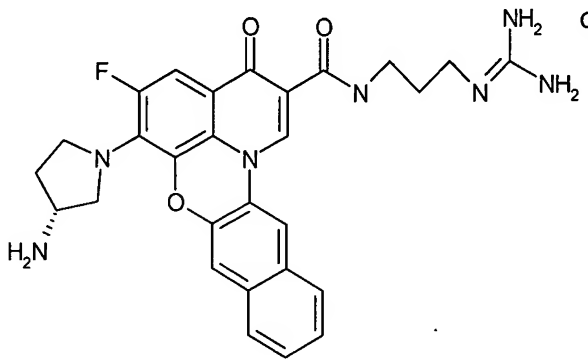
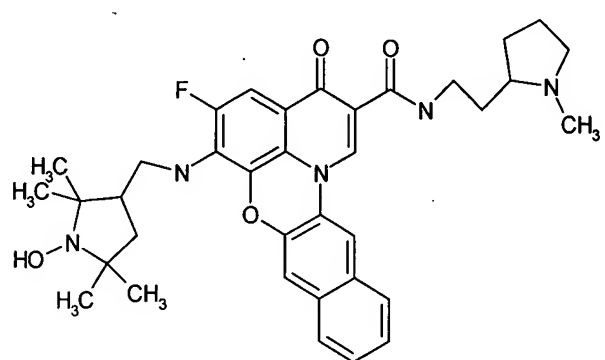


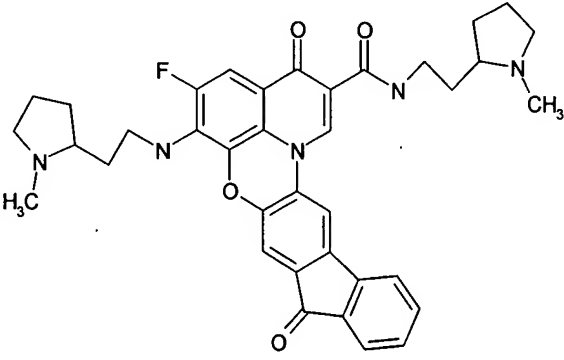
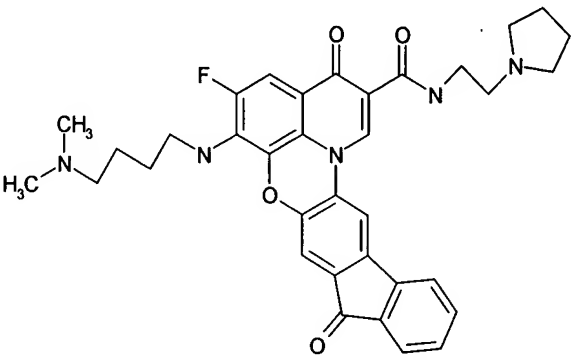
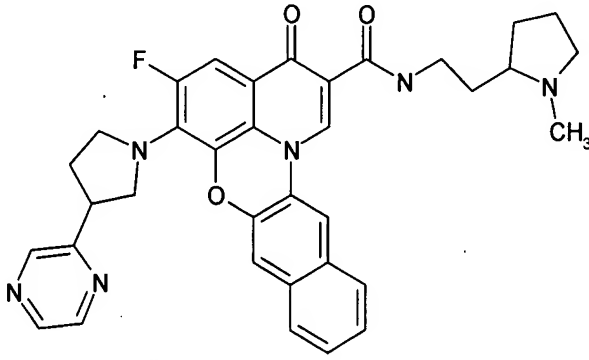
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
499		0.4	
500		0.375	5.60
501		0.375	4.20

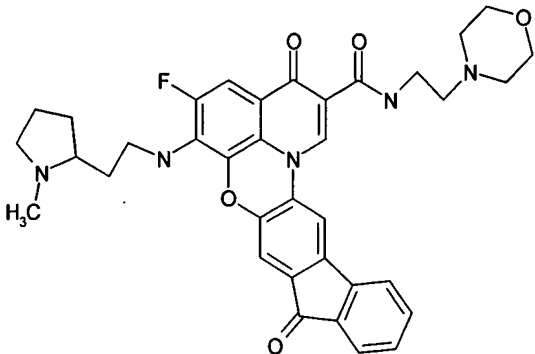
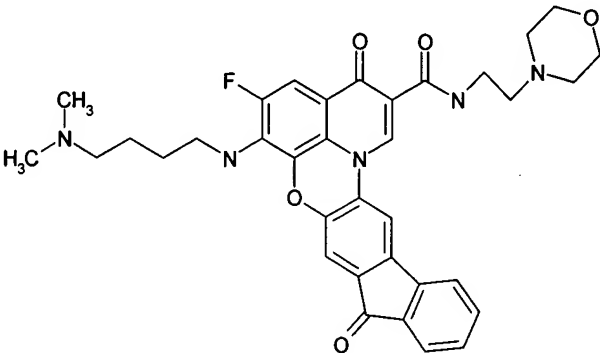
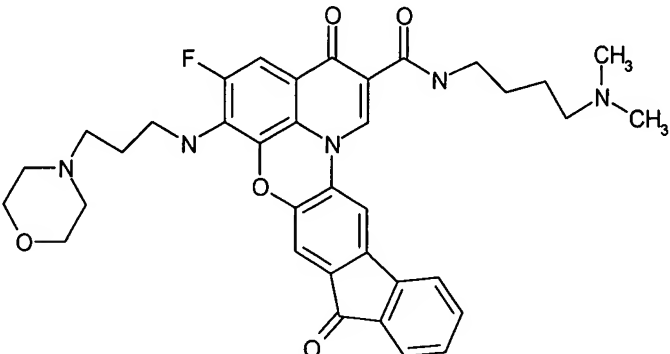
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
502		0.375	4.00
503		0.375	4.00
504		0.375	3.40

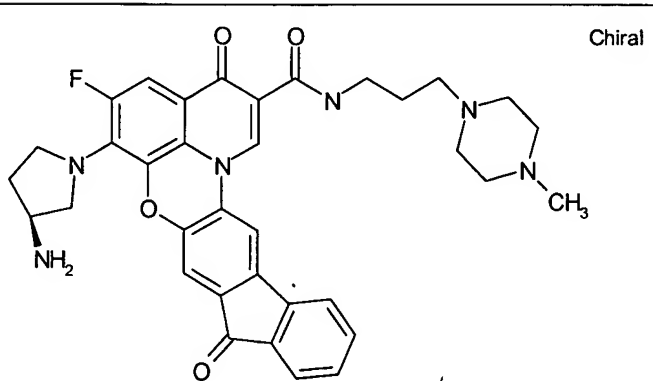
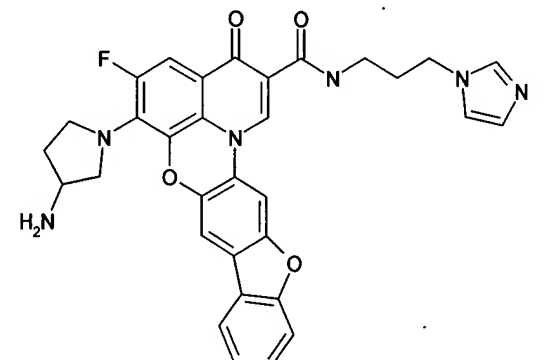
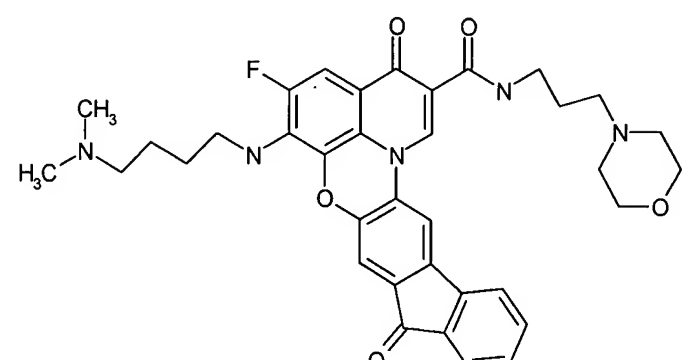




	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
511	 <p>Chiral</p>	0.375	3.10
512	 <p>Chiral</p>	0.375	3.10
513		0.375	3.10

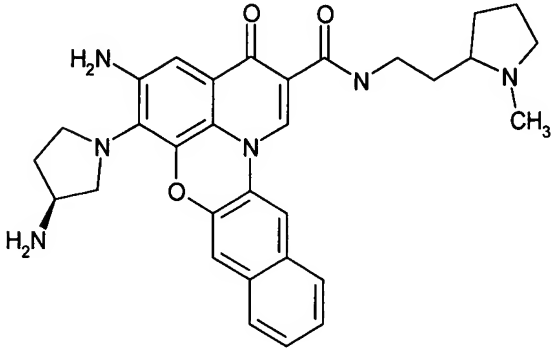
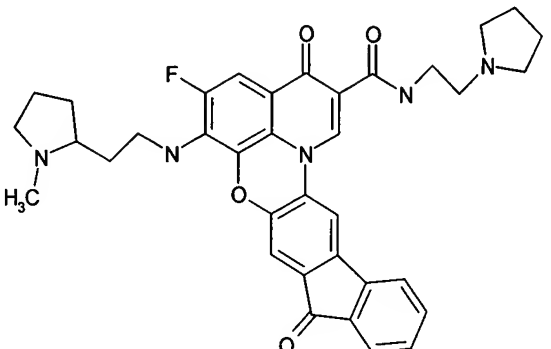
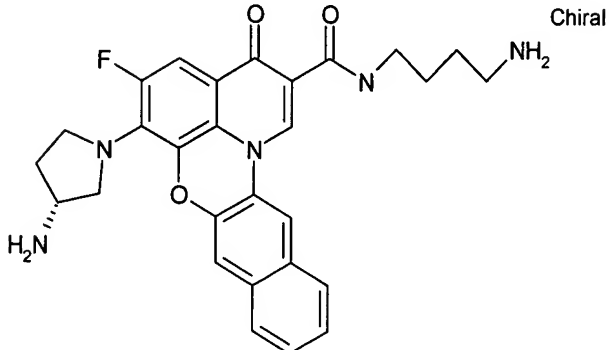
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
514		0.375	2.90
515		0.375	2.50
516		0.375	2.30

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
517		0.375	2.20
518		0.375	2.20
519		0.375	2.10

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
520	<p style="text-align: right;">Chiral</p> 	0.375	1.90
521		0.375	1.70
522		0.375	1.70

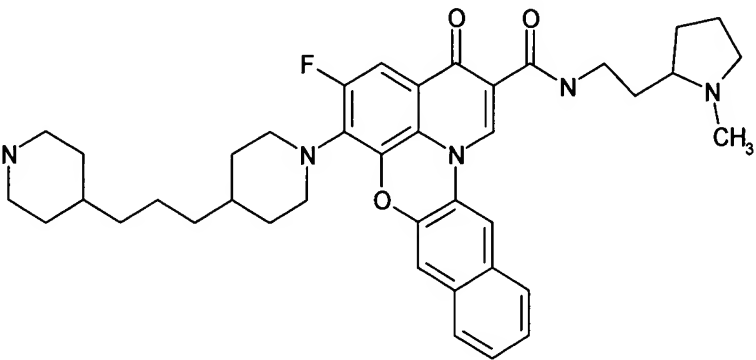
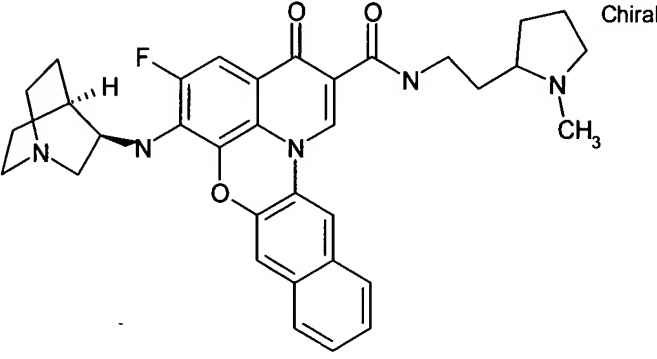
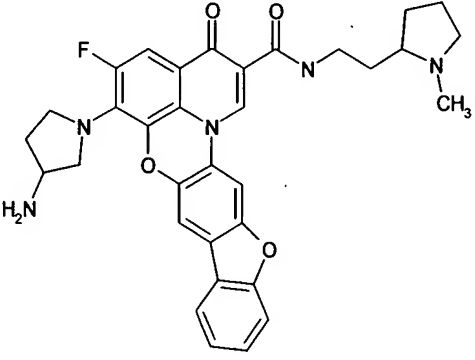


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
523		0.375	1.60
524		0.375	1.50
525		0.375	1.,2

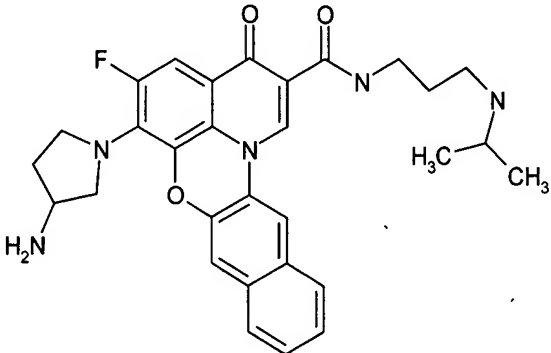
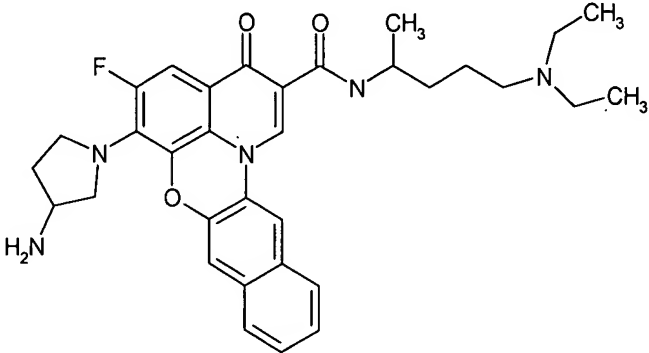
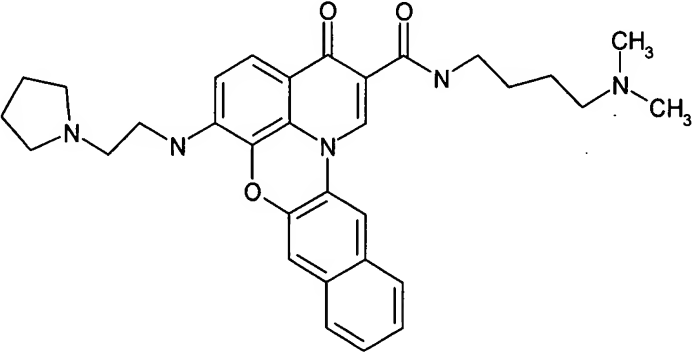
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
526		0.375	0.90
527		0.375	0.79
528		0.375	0.75

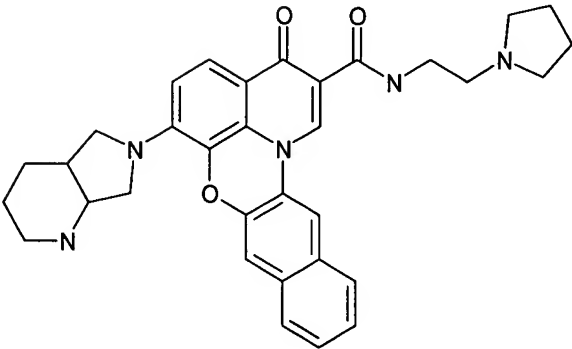
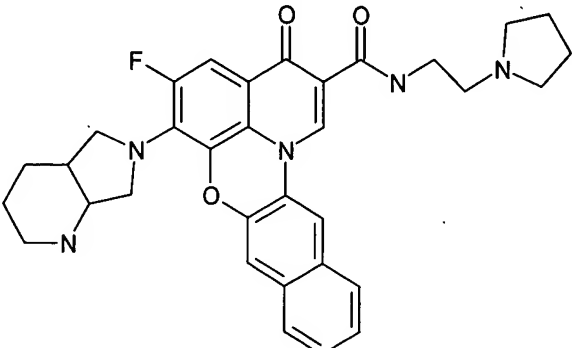
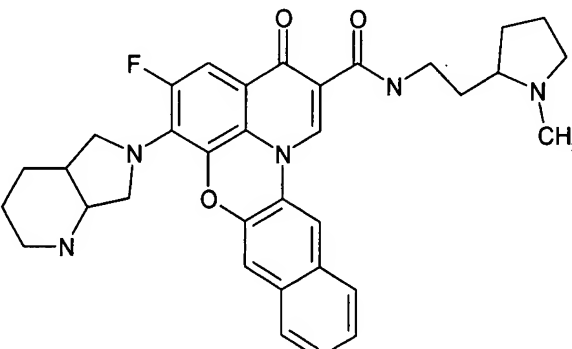
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
529		0.375	0.75
530		0.375	0.72
531		0.375	0.48

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
532		0.375	0.44
533		0.375	0.40
534		0.375	0.40

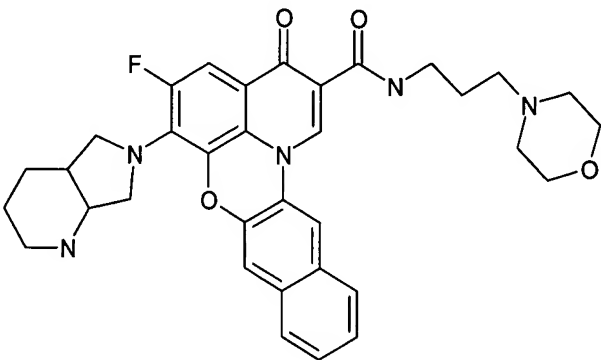
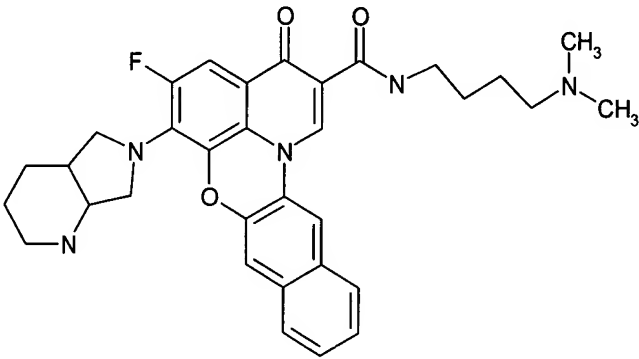
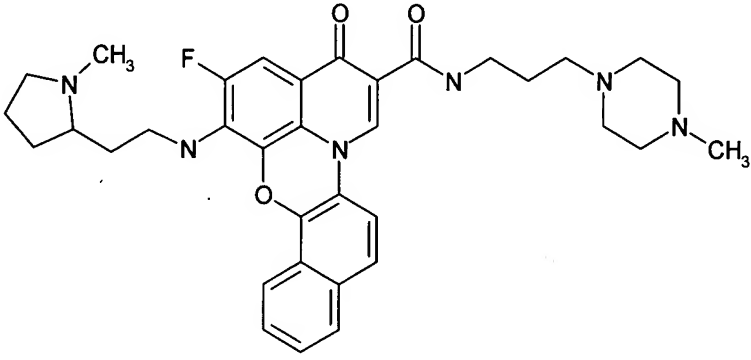
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
535		0.375	0.31
536		0.375	0.31
537		0.375	0.29

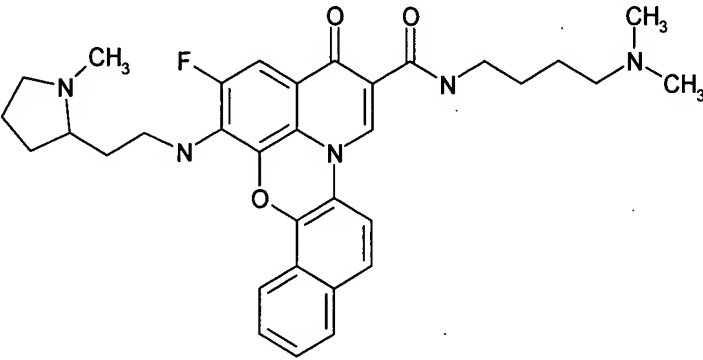
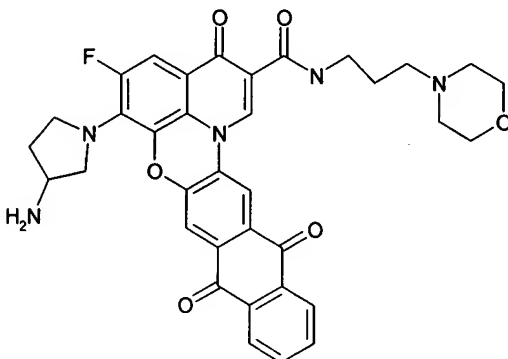
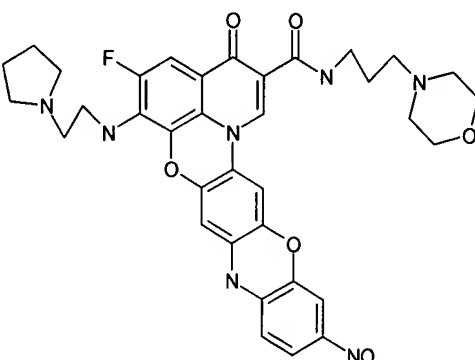
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
538		0.375	0.28
539		0.375	0.28
540		0.375	0.27

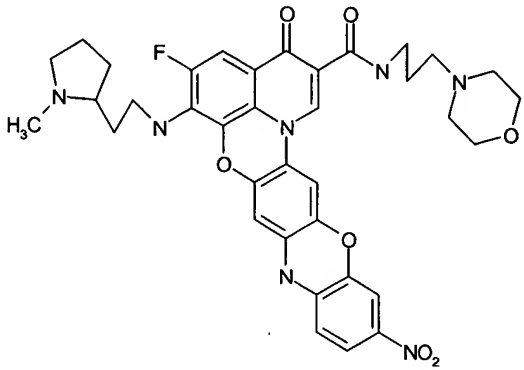
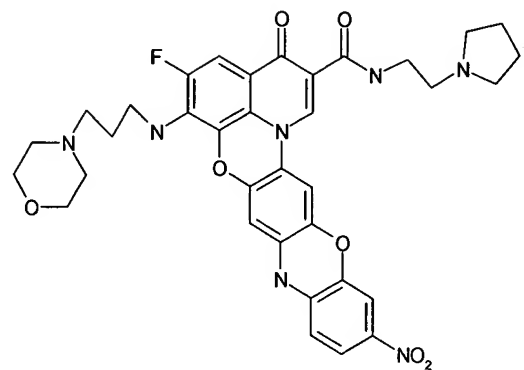
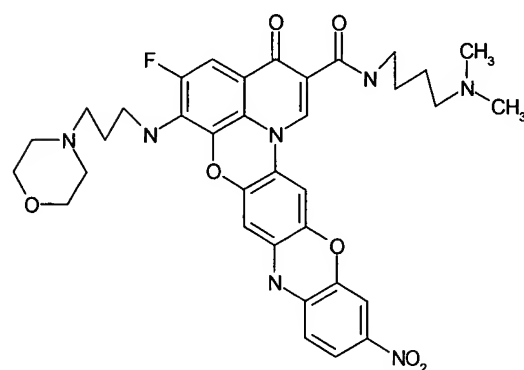
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
541		0.375	0.27
542		0.375	0.23
543		0.375	0.20

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
544		0.375	0.20
545		0.375	0.15
546		0.375	0.10

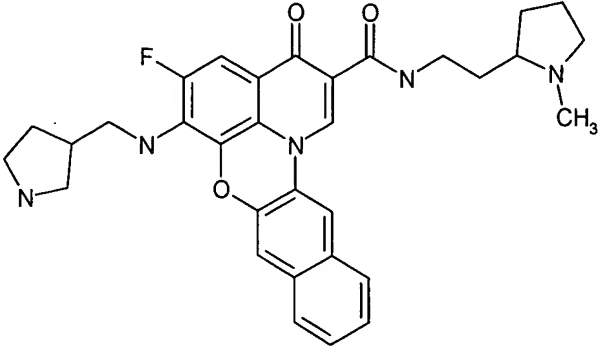
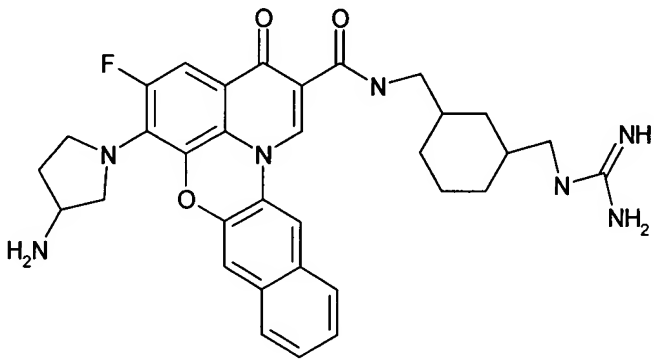
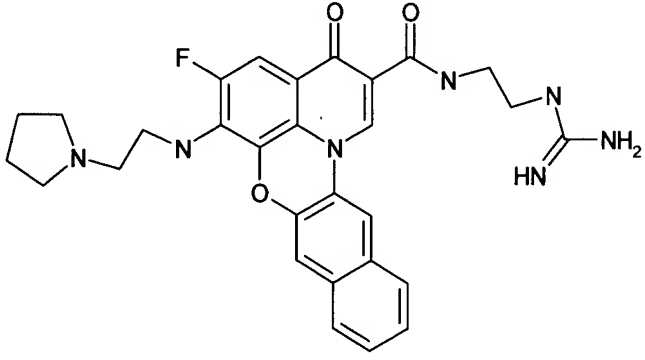


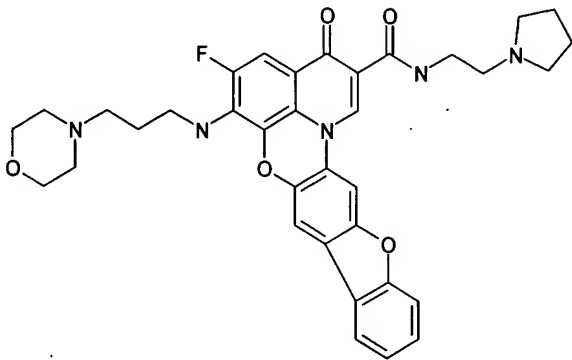
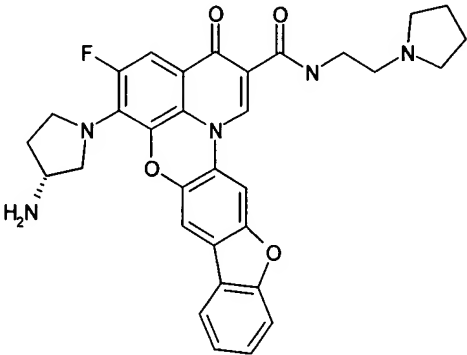
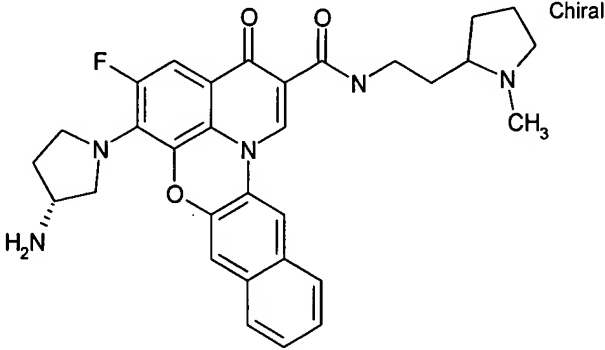
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
547		0.375	0.10
548		0.375	0.10
549		0.375	

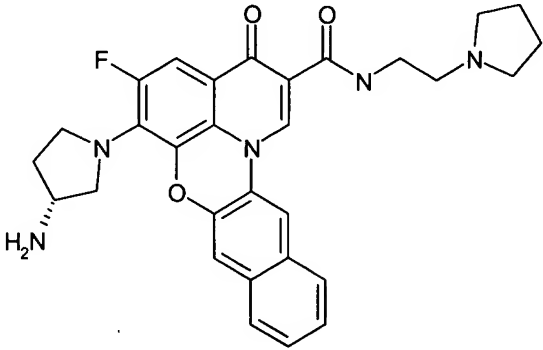
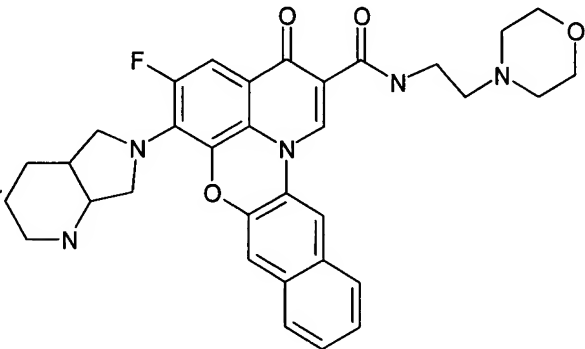
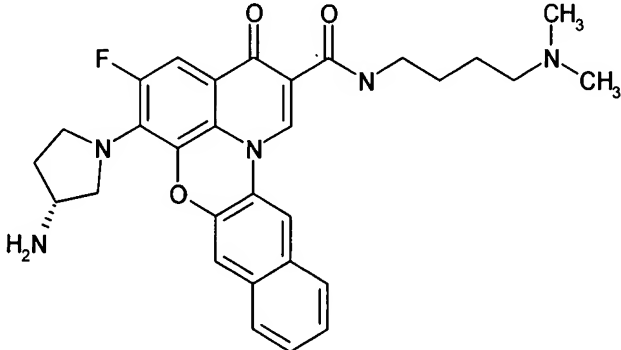
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
550		0.375	
551		0.375	
552		0.375	

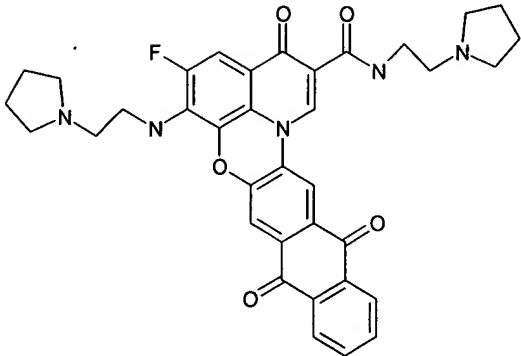
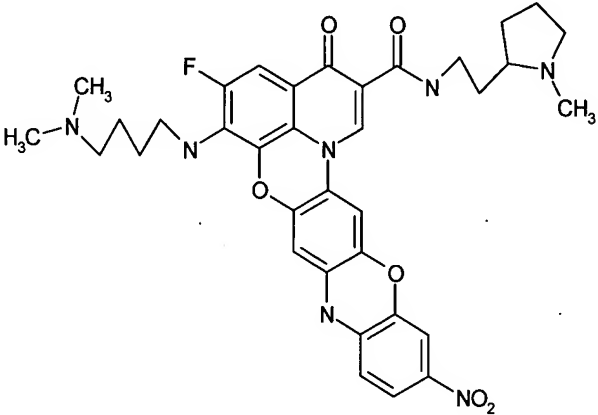
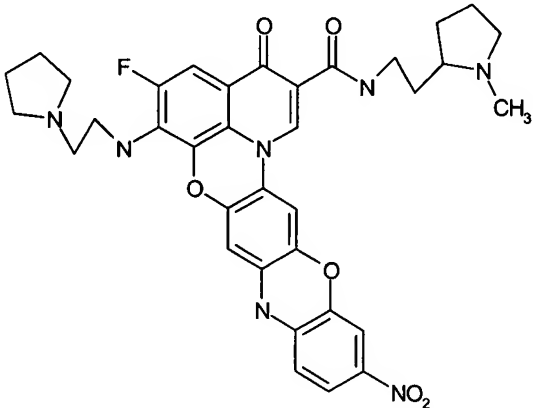
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
553		0.375	
554		0.375	
555		0.375	

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
556		0.375	
557		0.375	
558		0.375	

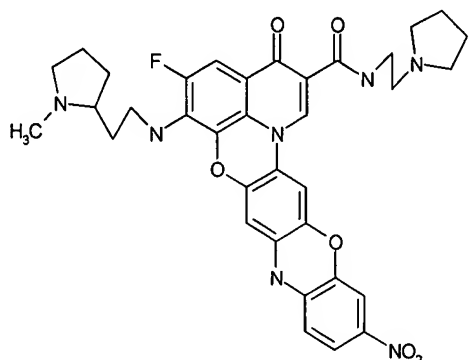
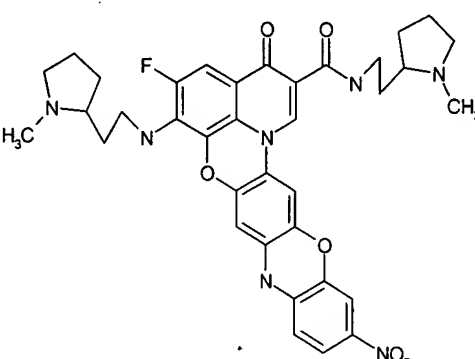
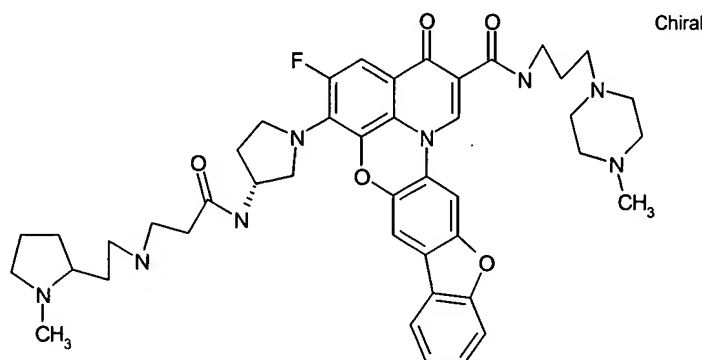
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
559		0.375	
560		0.37	
561		0.34	

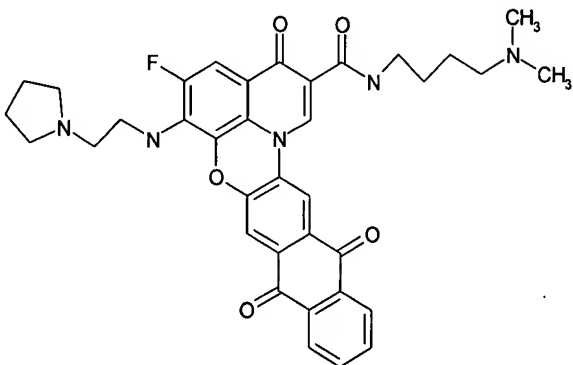
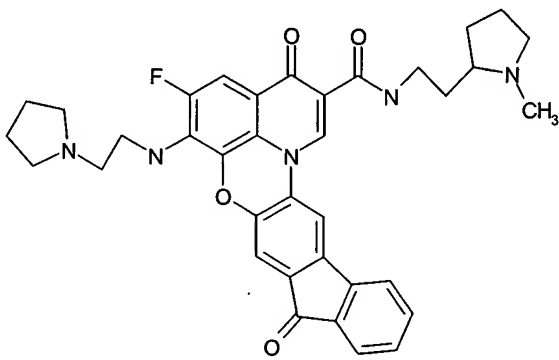
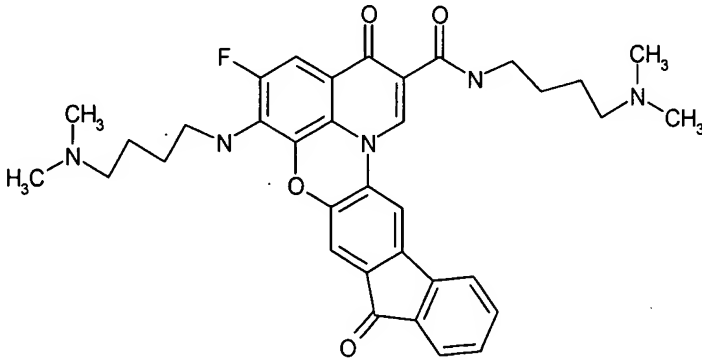
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
562		0.32	0.85
563		0.25	0.31
564		0.25	0.29

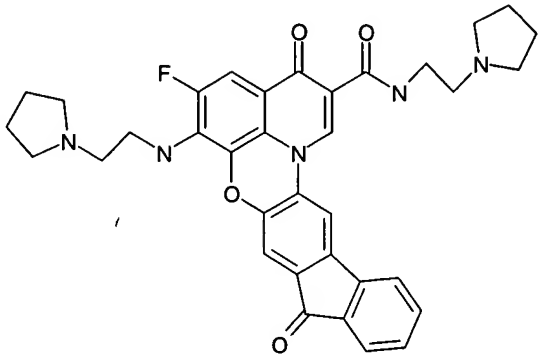
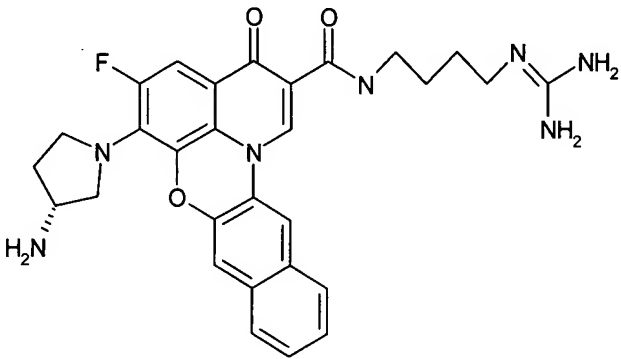
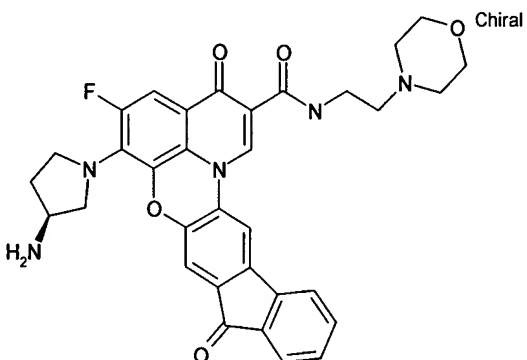
	Structure	Stop Data c-Myc $\mu\text{M}$	MTS Data Hella $\mu\text{M}$
565		0.25	0.20
566		0.25	0.03
567		0.25	

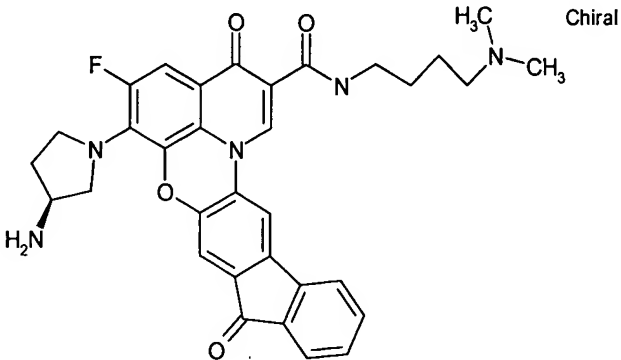
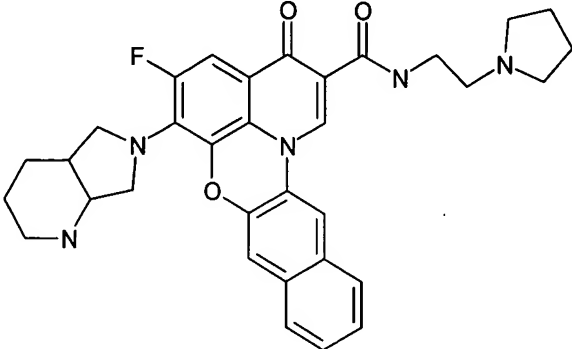
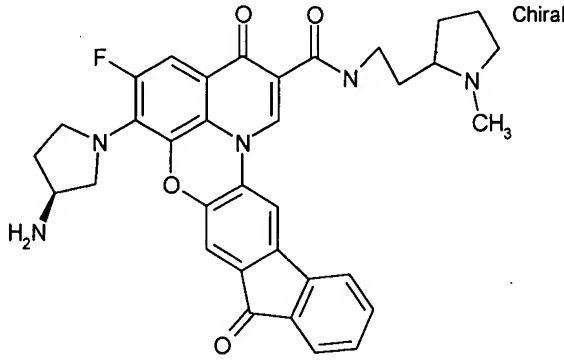
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
568		0.22	4.10
569		0.18	7.80
570		0.18	6.80



	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
571		0.18	4.80
572		0.18	4.80
573		0.18	4.50

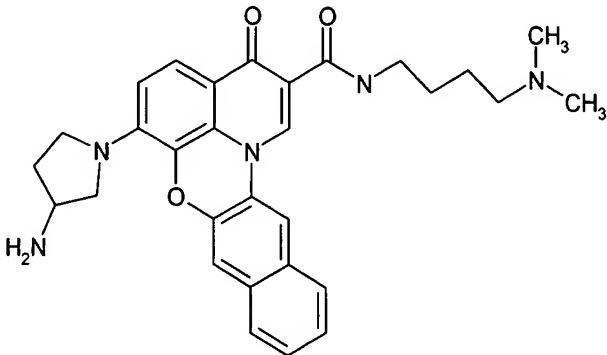
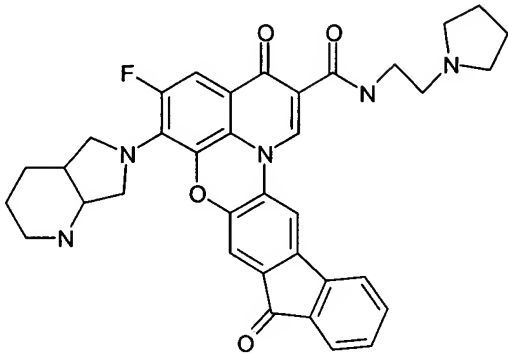
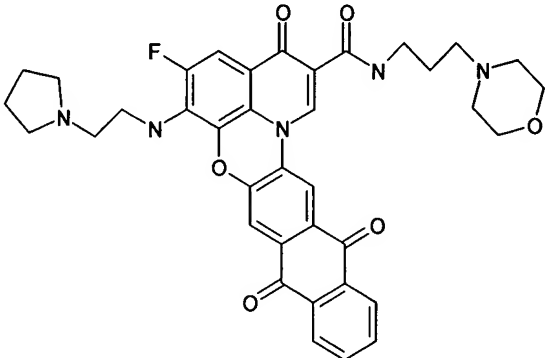
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
574		0.18	4.00
575		0.18	2.10
576		0.18	2.10

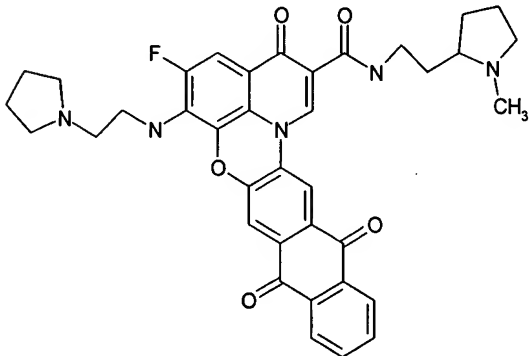
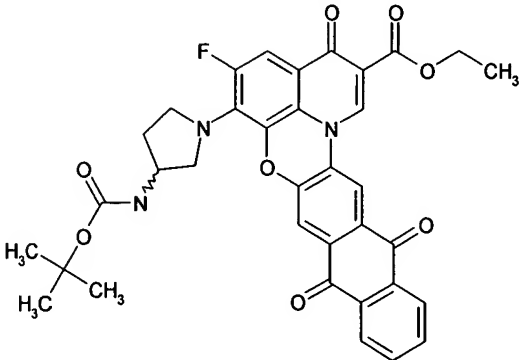
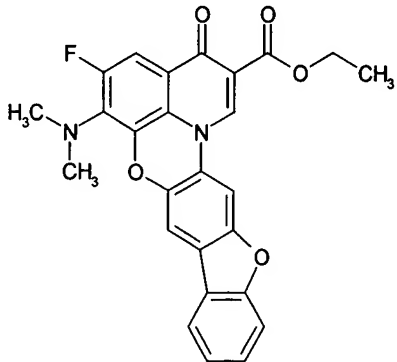
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
577		0.18	1.10
578		0.18	0.58
579		0.18	0.49

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
580		0.18	0.30
581		0.18	0.30
582		0.18	0.28

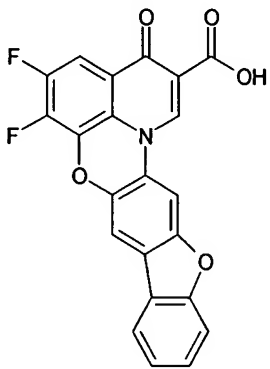
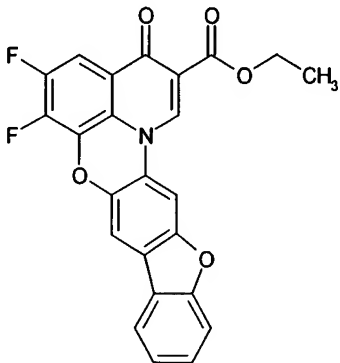
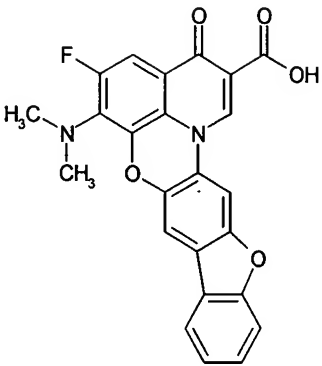
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
583	<p>Chiral</p>	0.18	0.25
584		0.18	0.19
585		0.18	

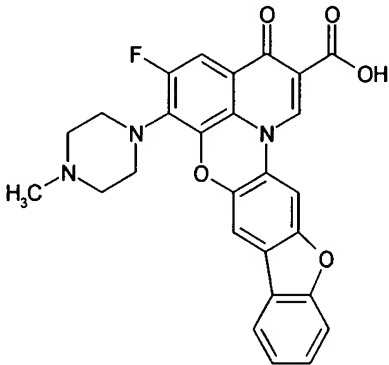
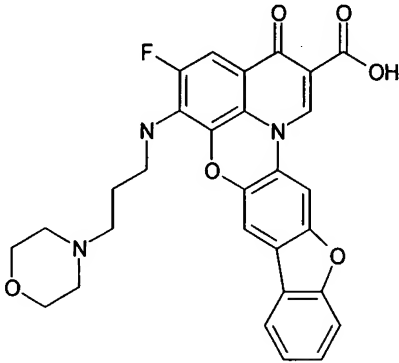
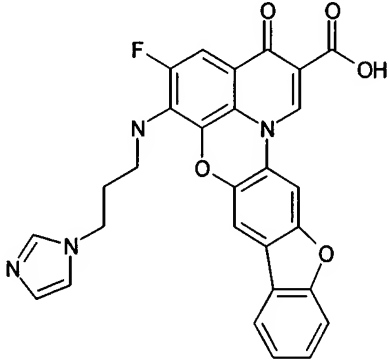
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
586		0.18	
587		0.18	
588		0.18	

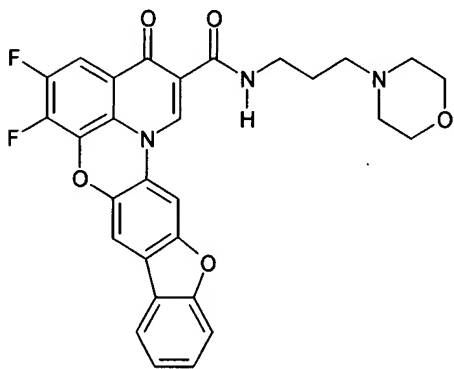
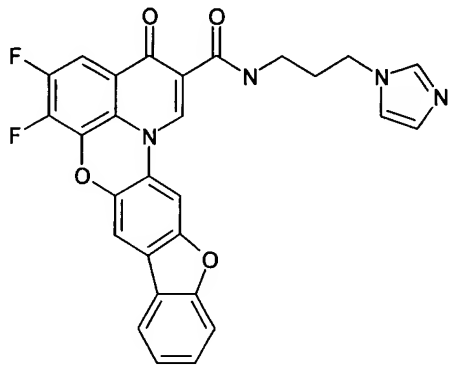
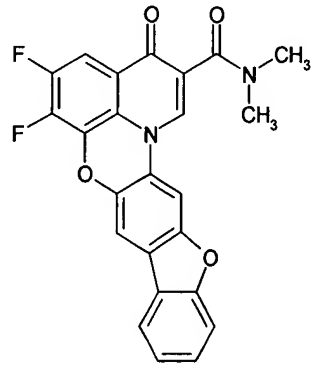
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
589		0.18	
590		0.18	
591		0.13	3.30

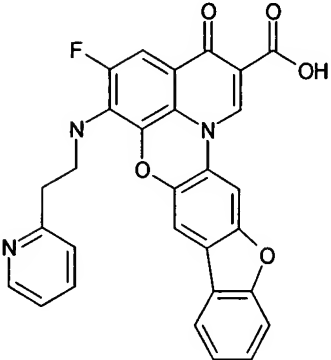
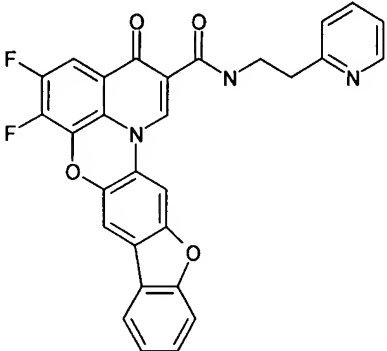
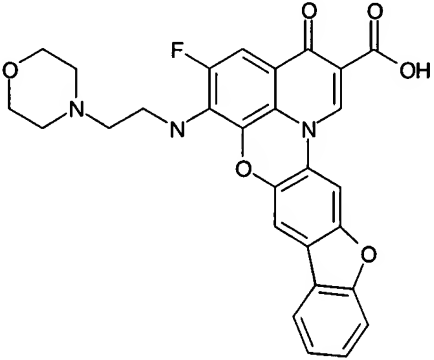
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
592		0.1	3.80
<b>Table 3</b>			
593			
594			

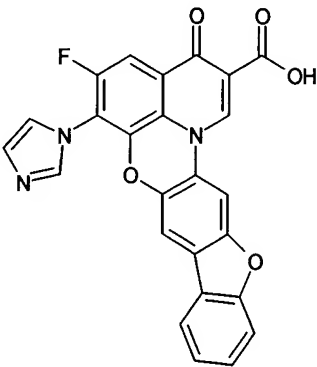
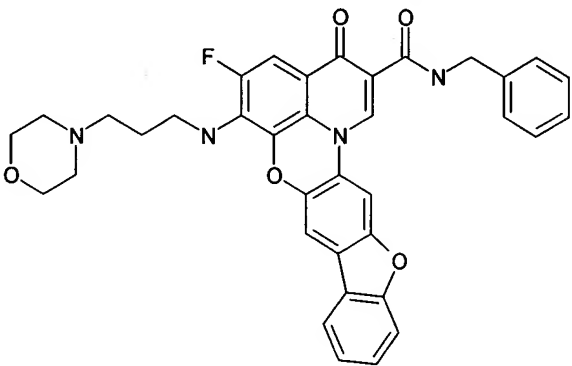
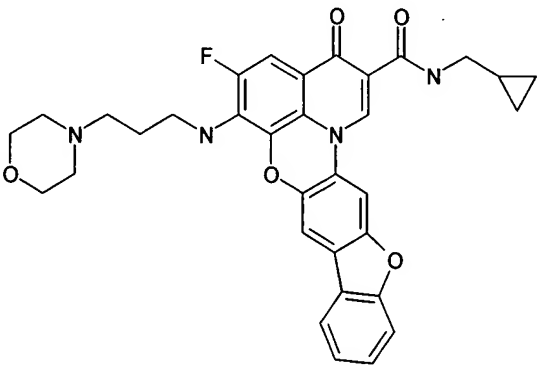


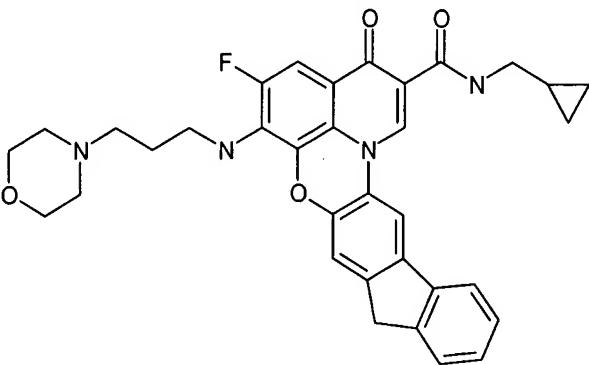
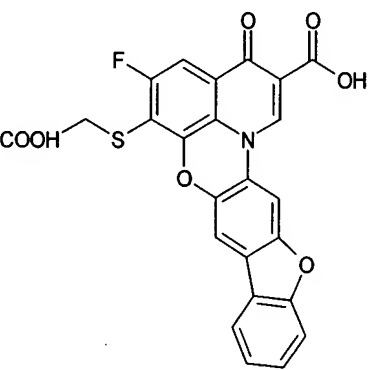
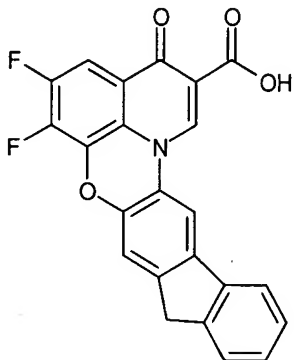
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
595			
596			
597			

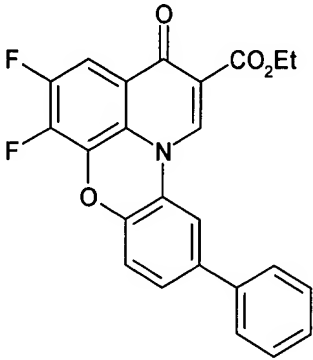
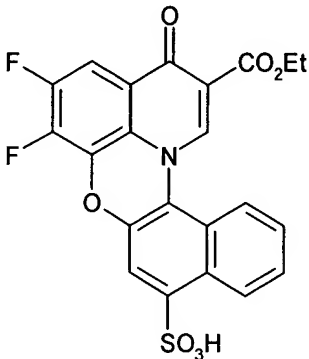
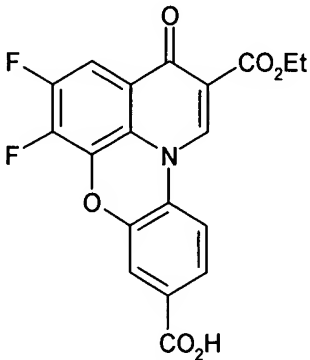
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
598			
599			
600			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
601			
602			
603			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
604			
605			
606			

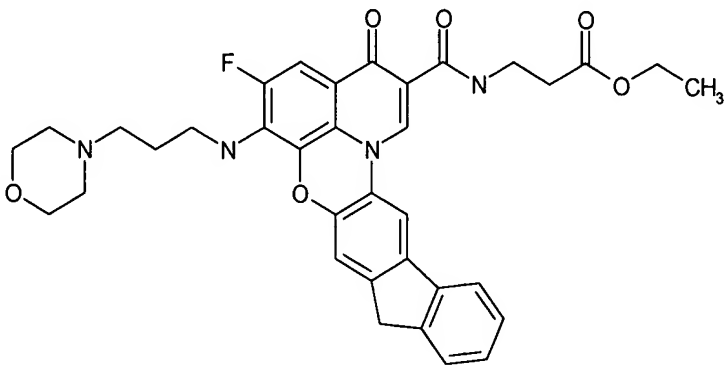
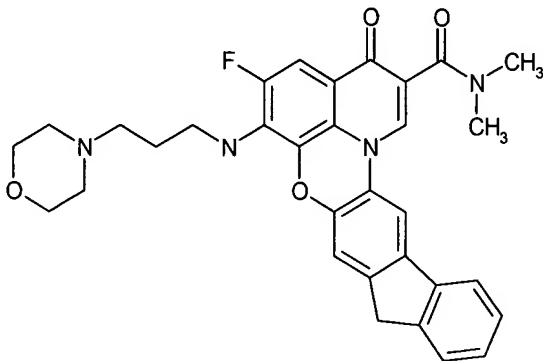
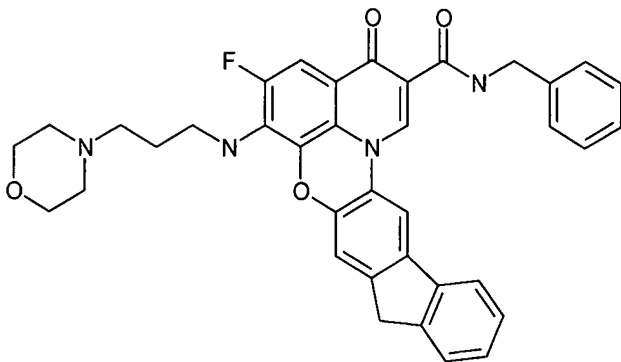
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
607			
608			
609			

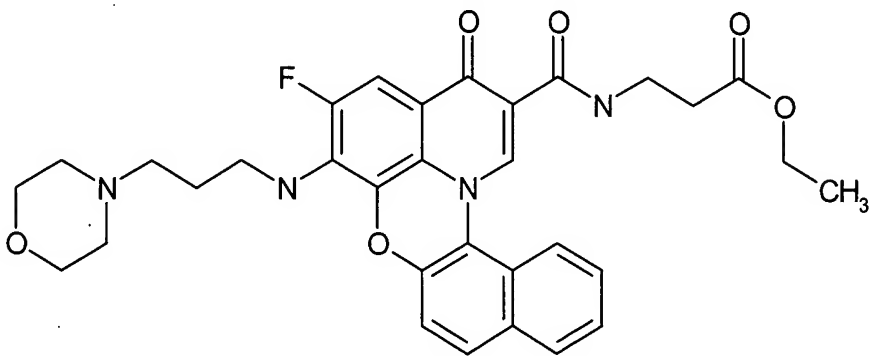
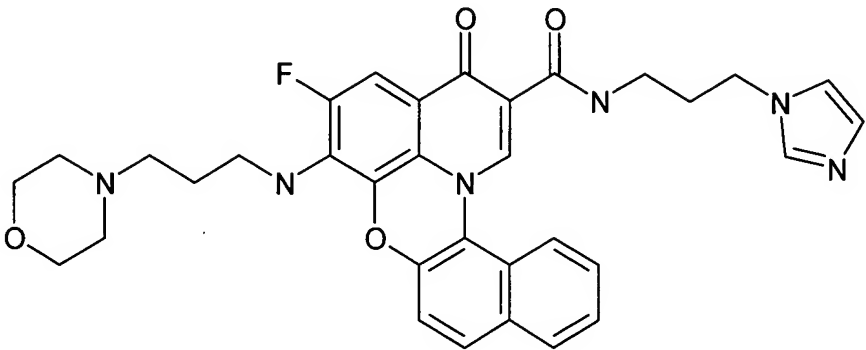
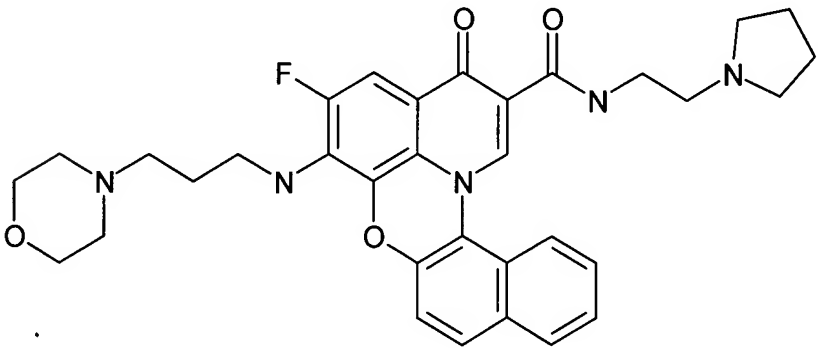
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
610			
611			
612			

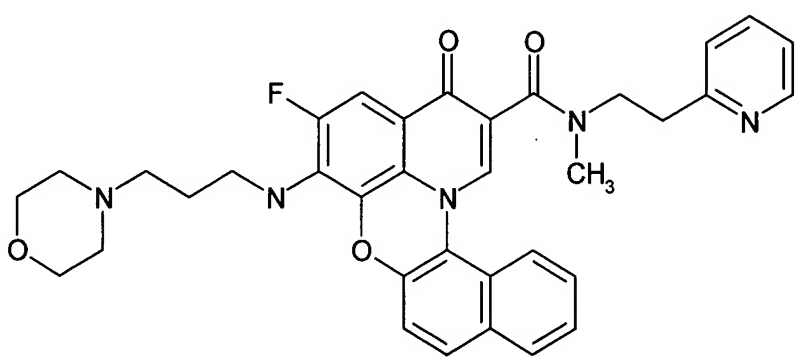
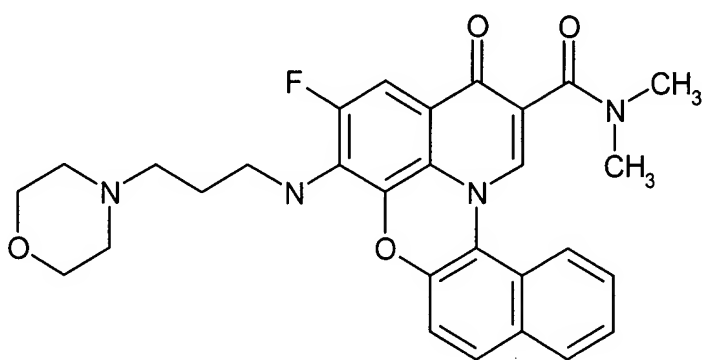
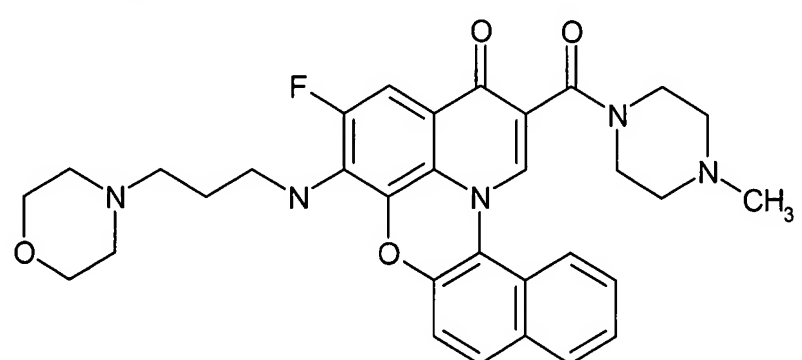
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
613			
614			
615			

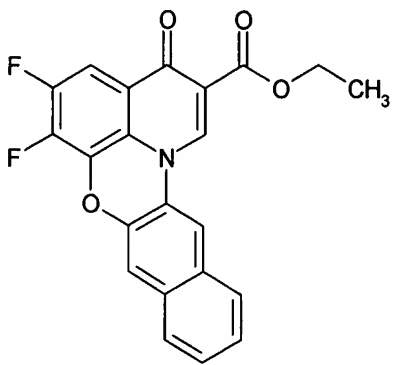
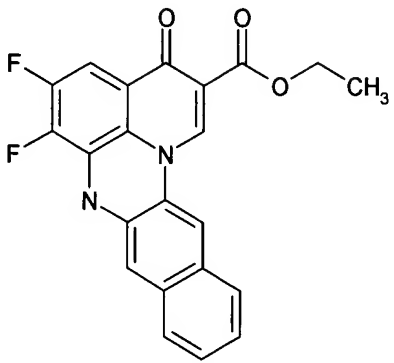
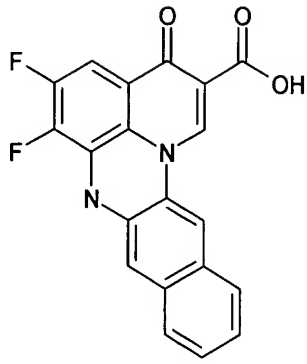
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
616			
617			
618			

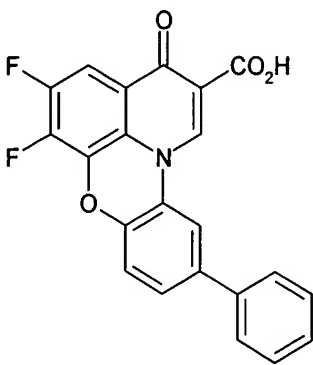
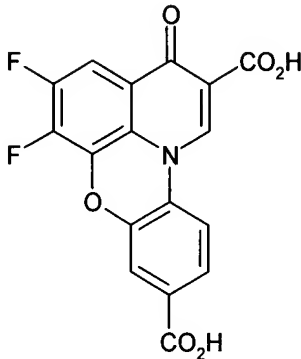
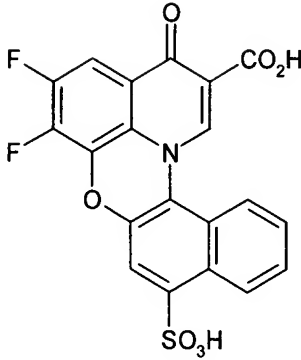


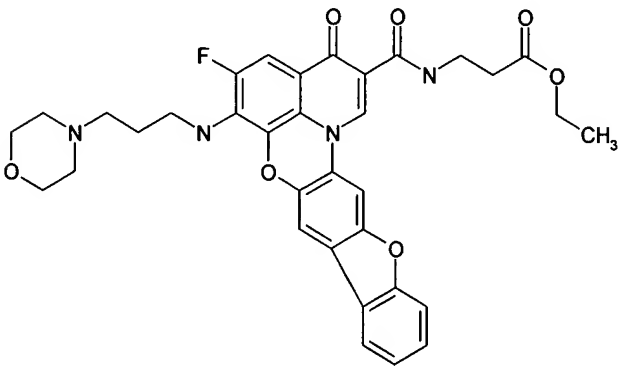
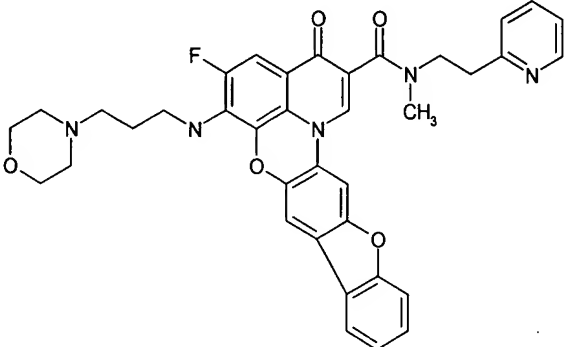
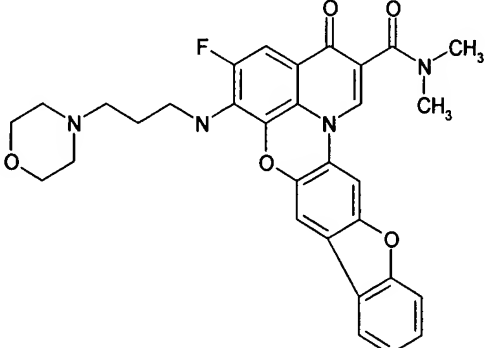
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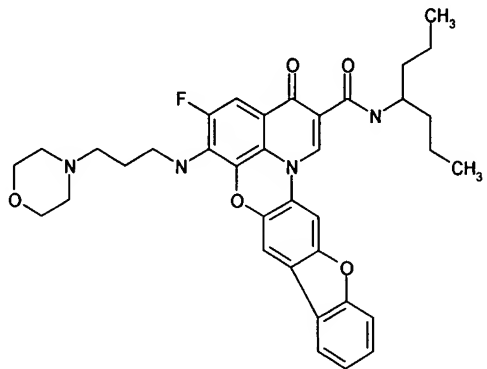
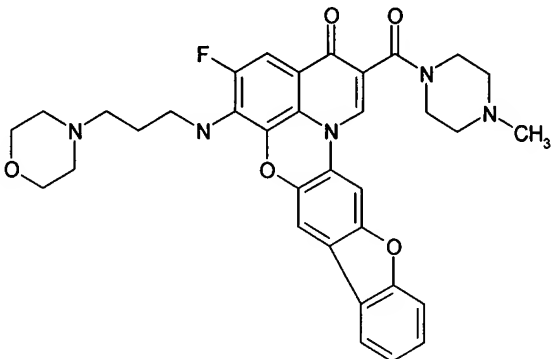
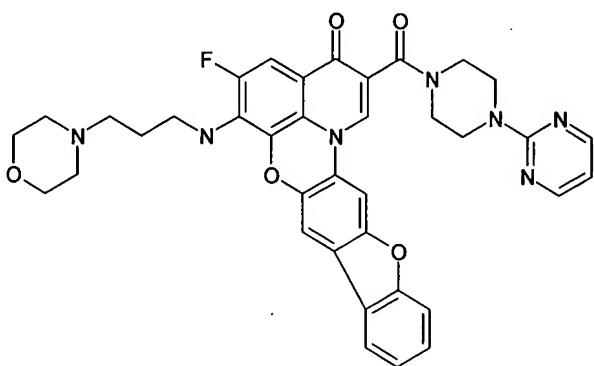
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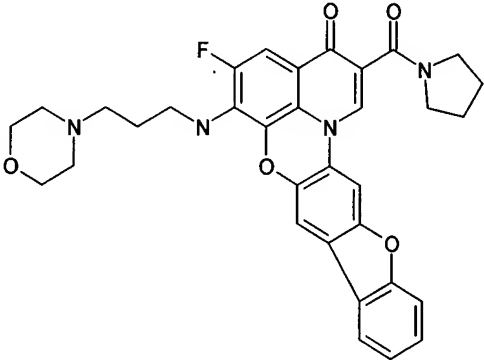
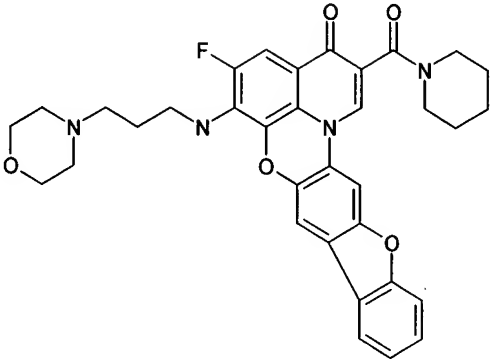
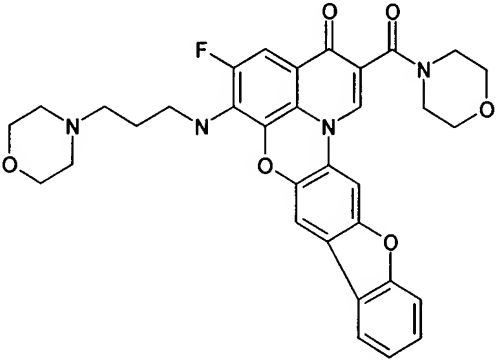
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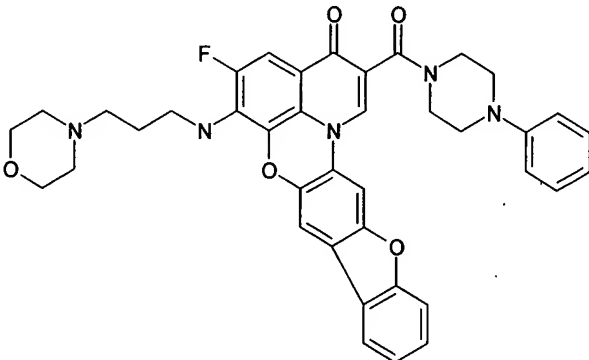
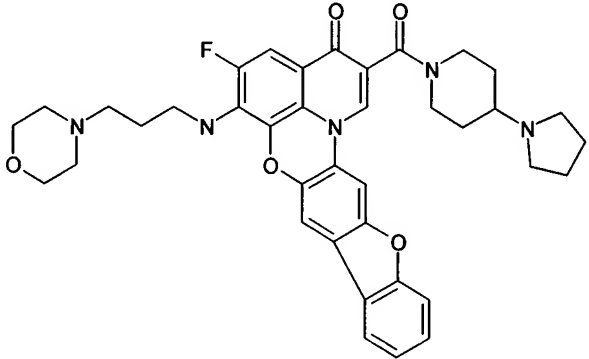
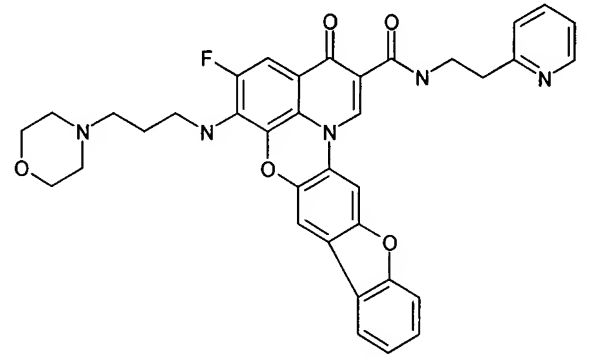
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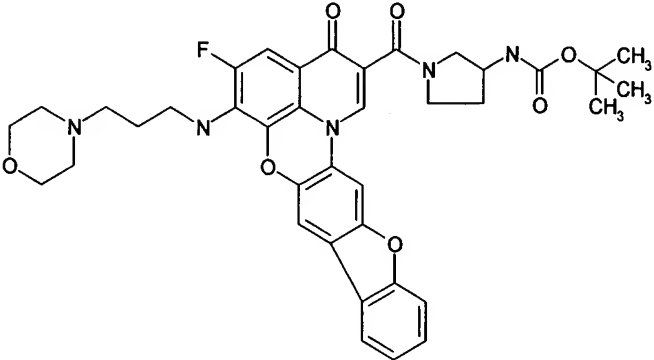
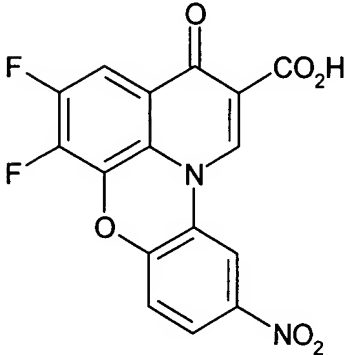
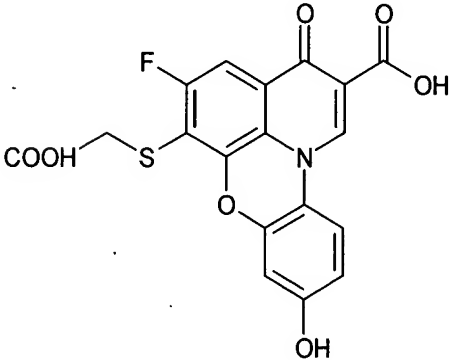
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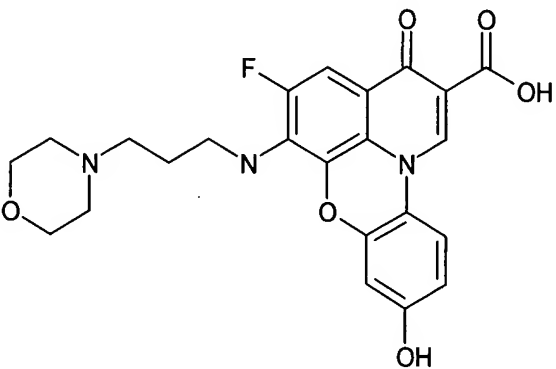
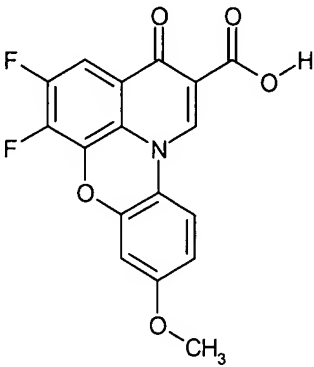
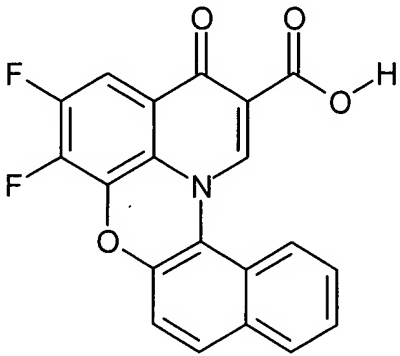
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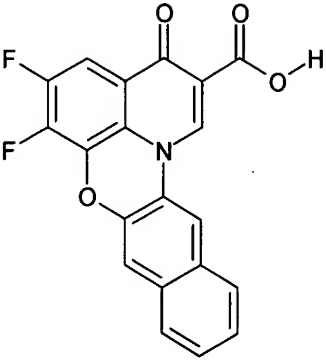
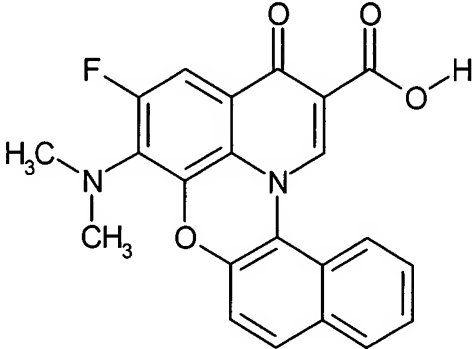
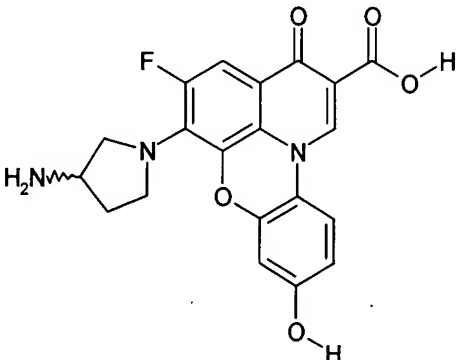
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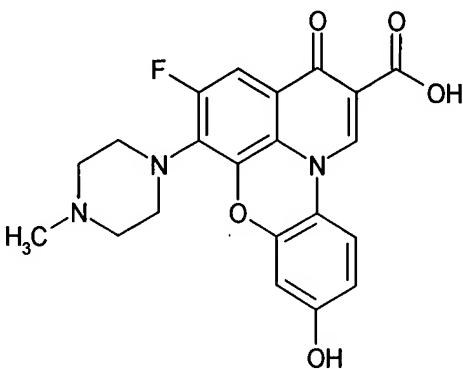
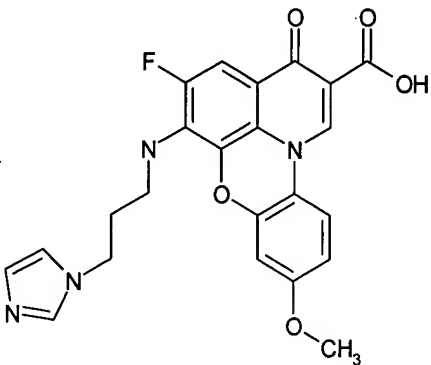
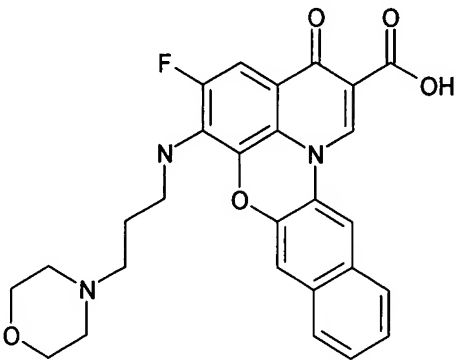
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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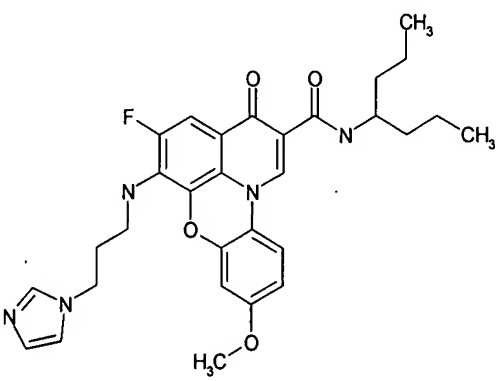
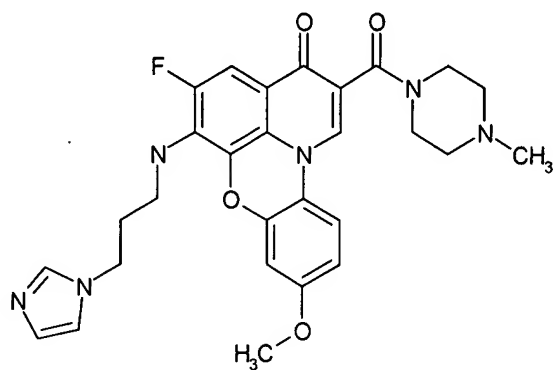
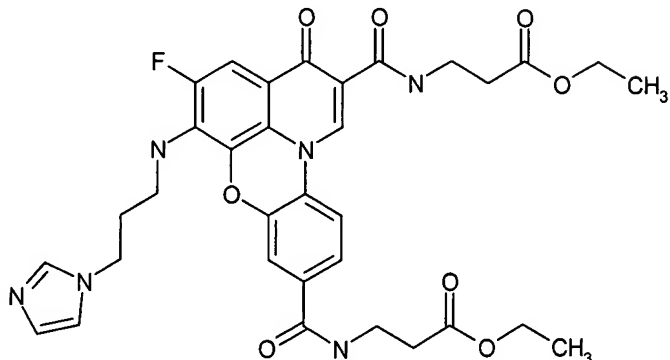
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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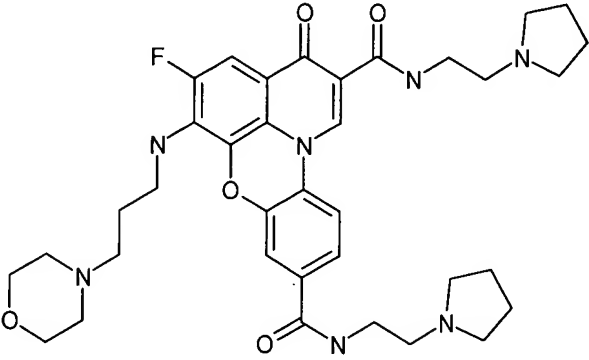
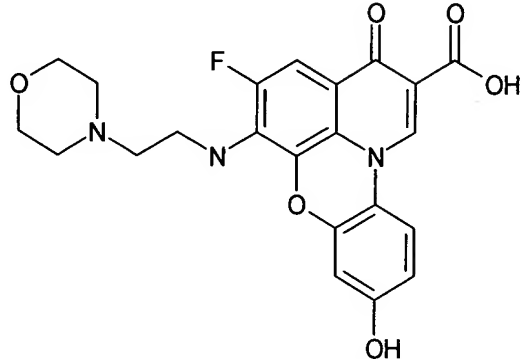
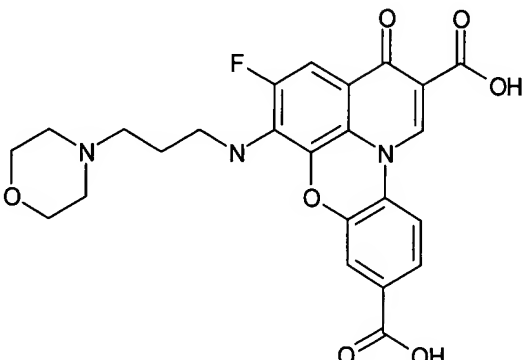
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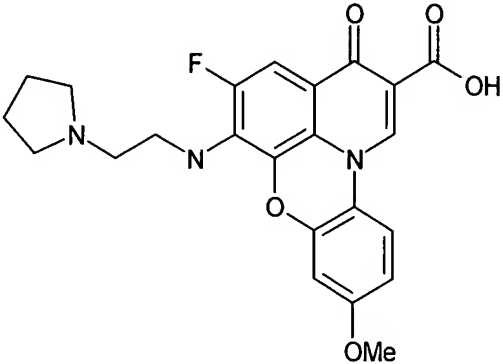
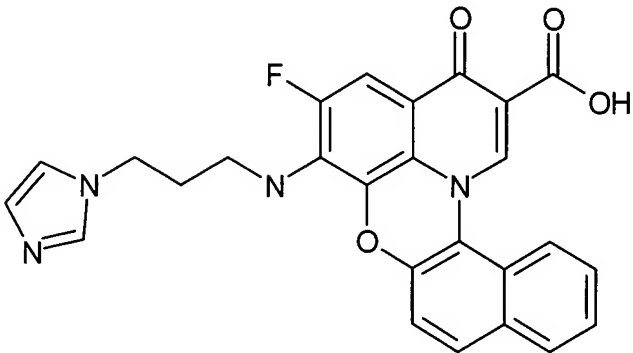
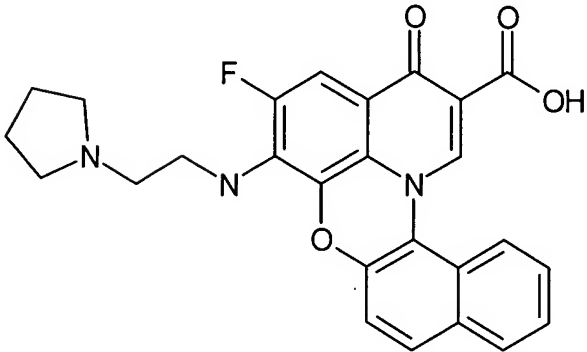


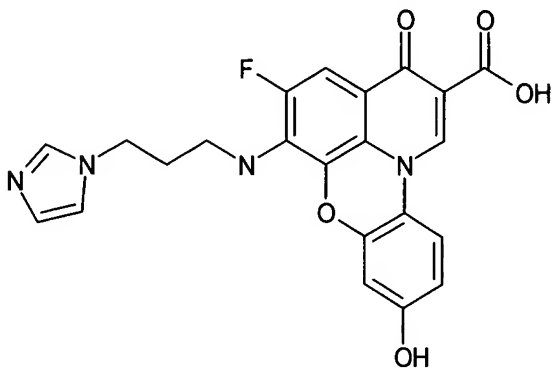
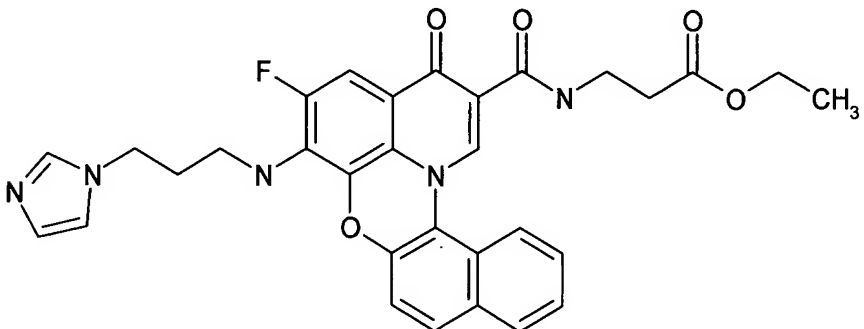
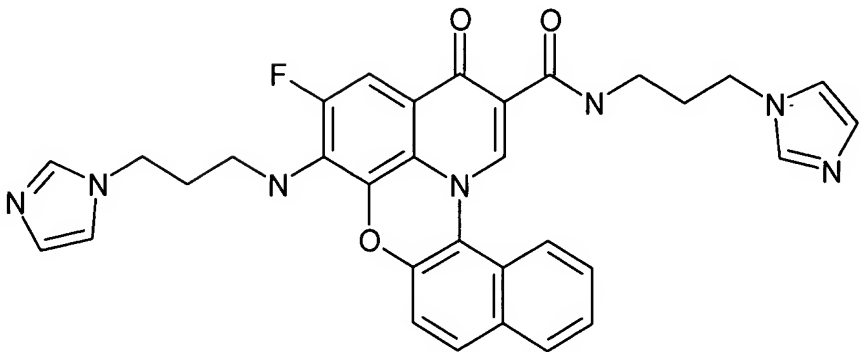
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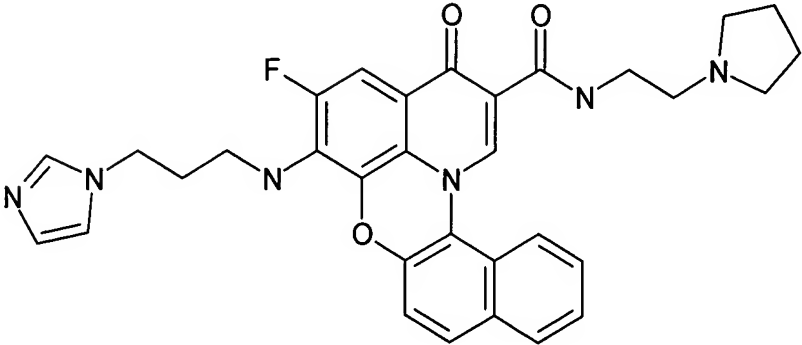
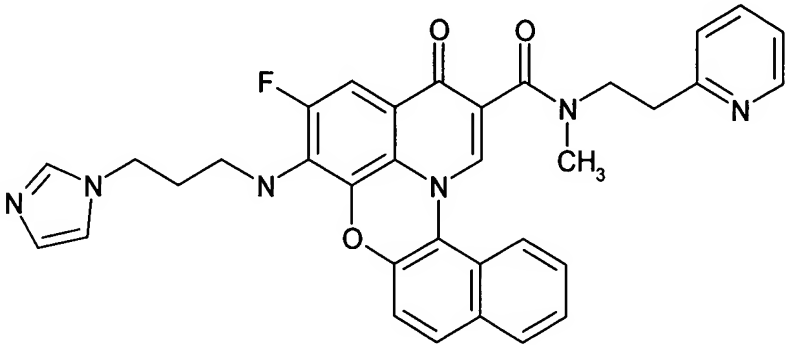
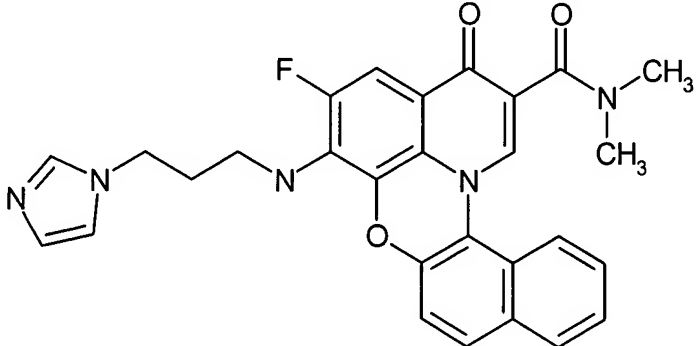
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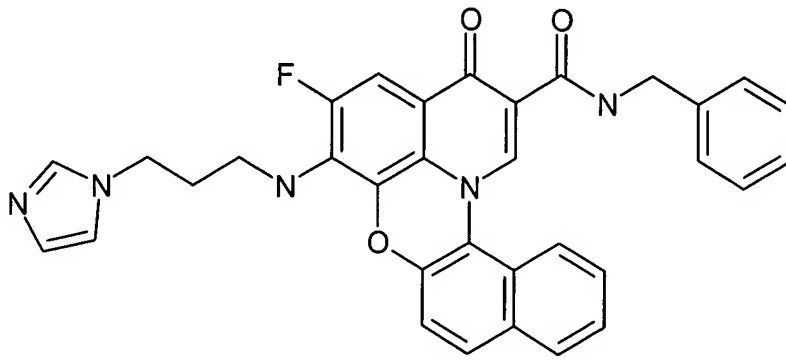
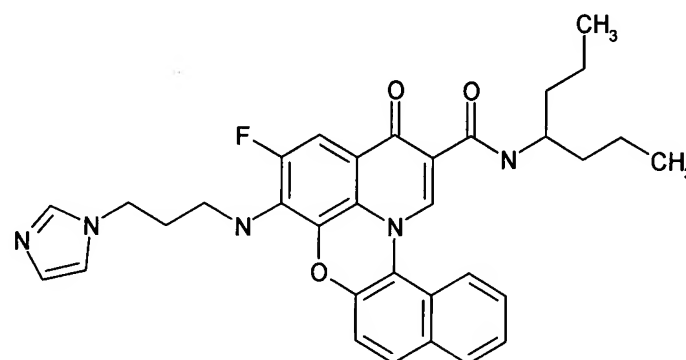
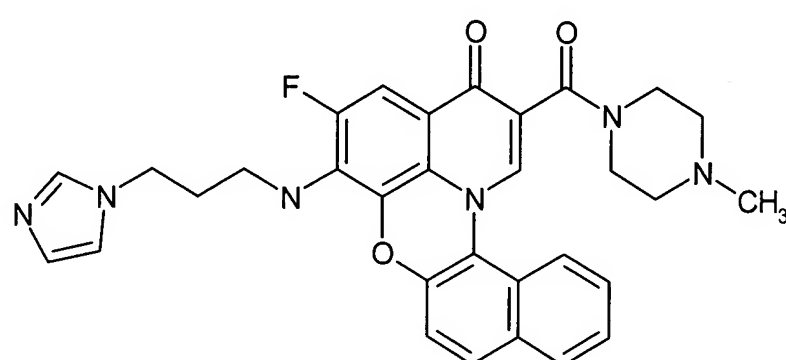
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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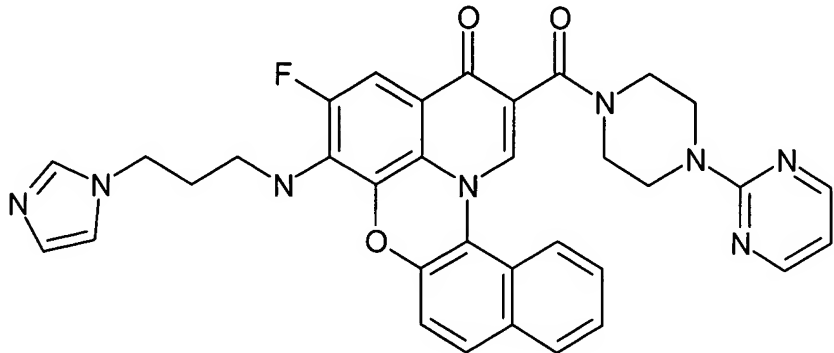
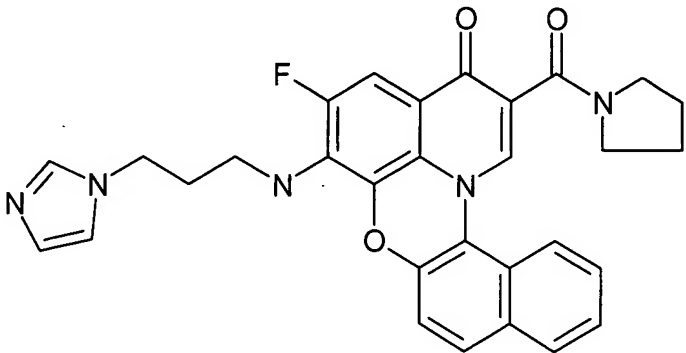
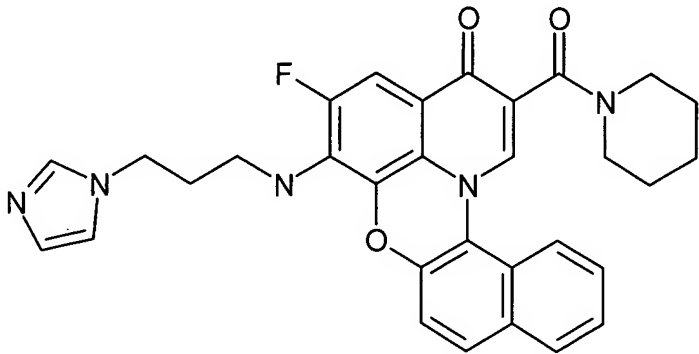
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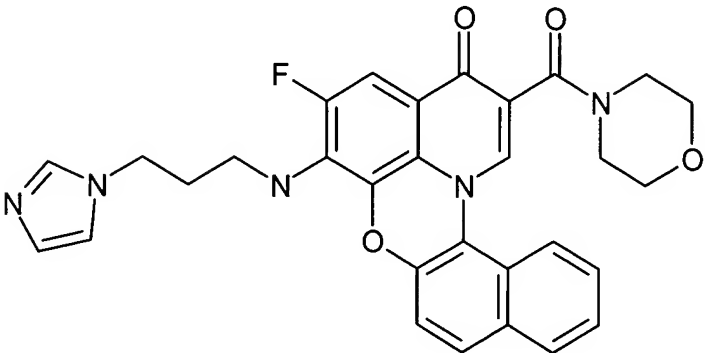
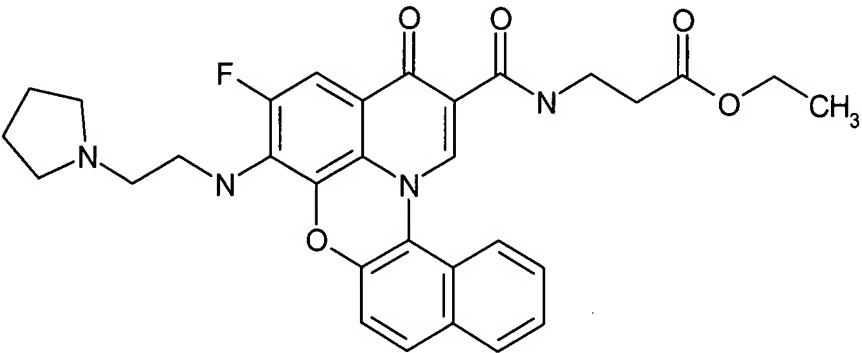
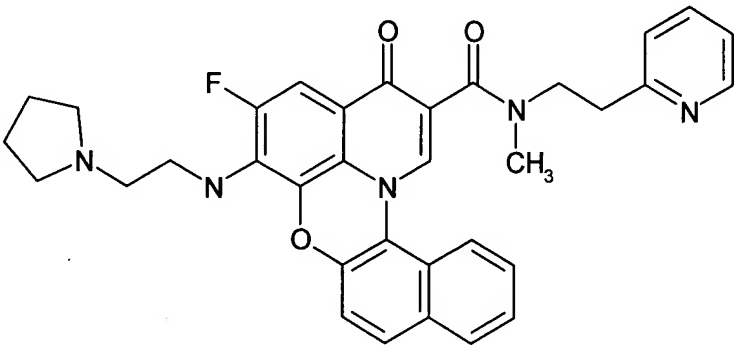
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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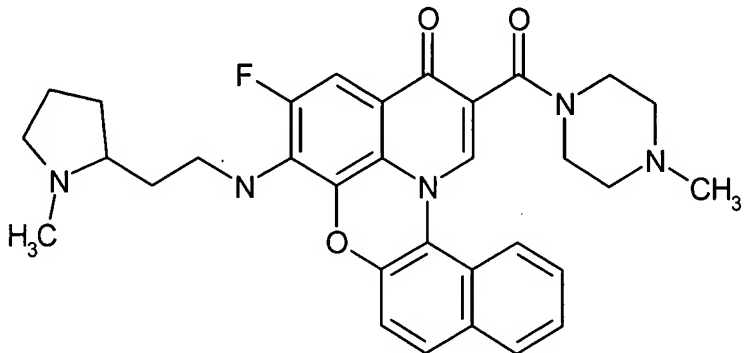
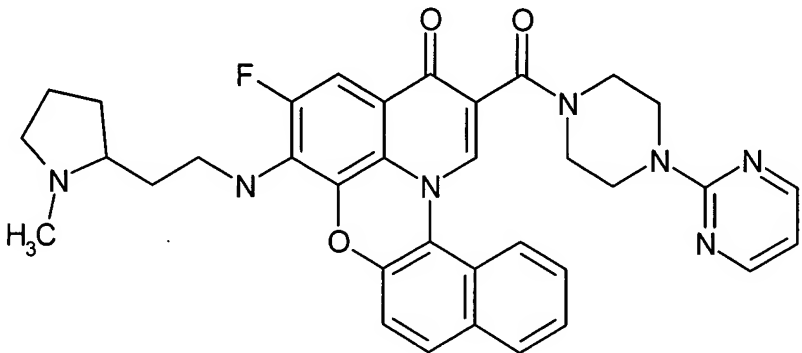
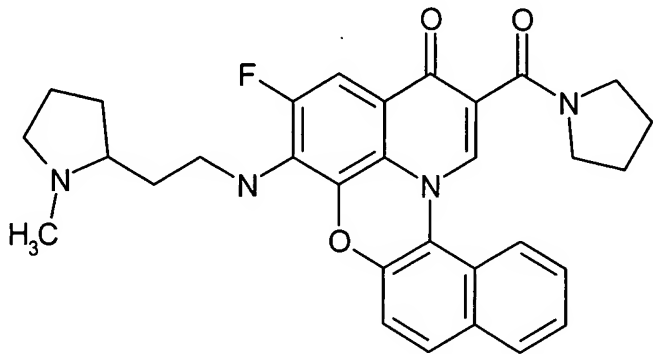
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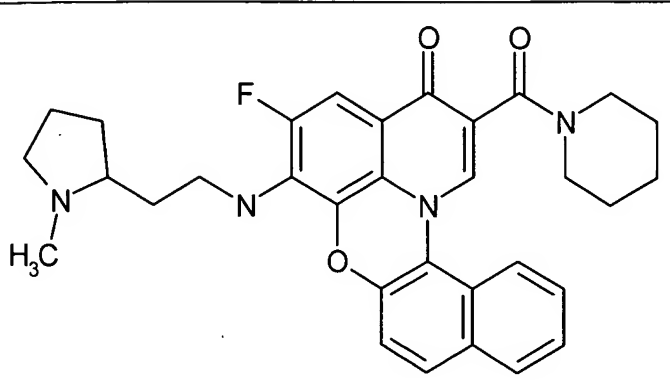
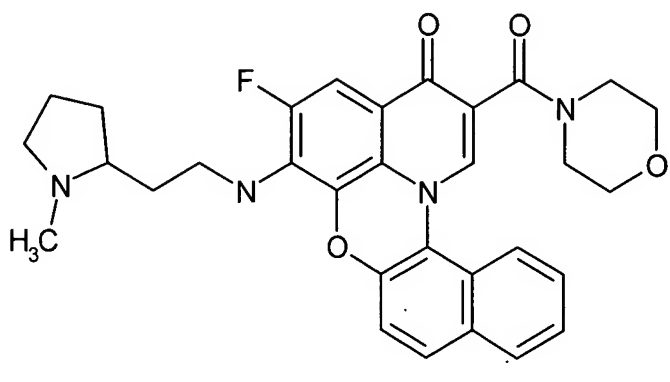
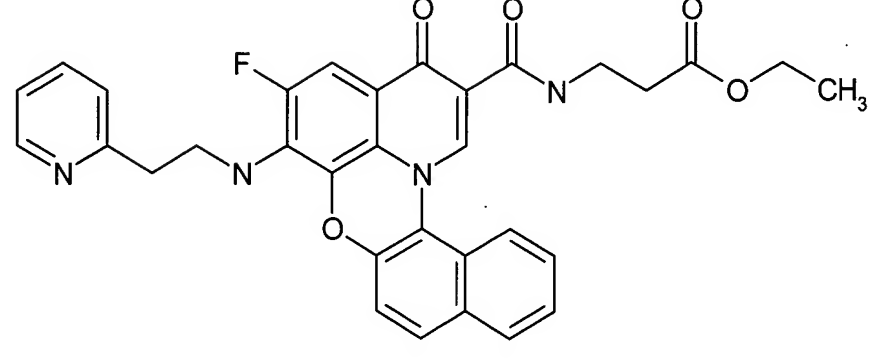
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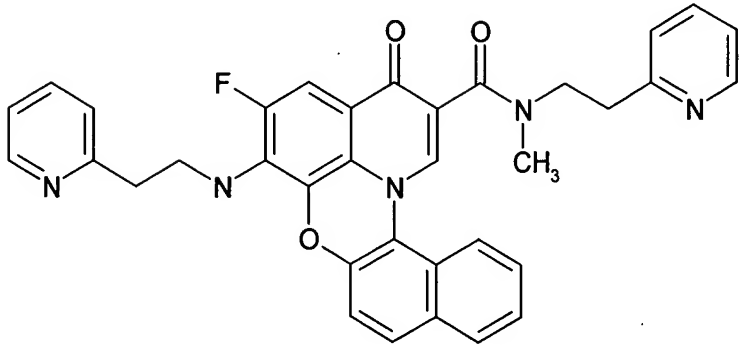
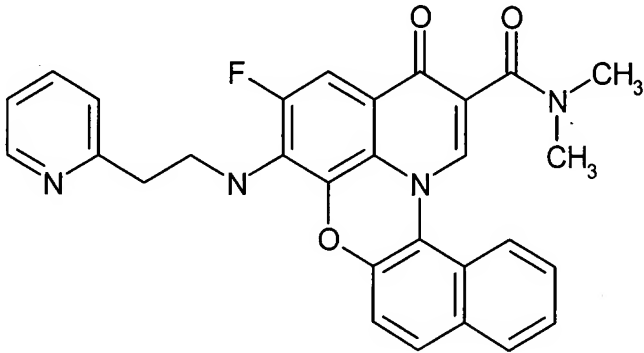
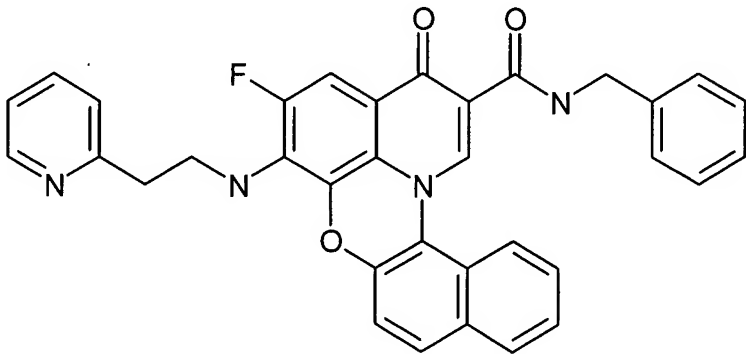
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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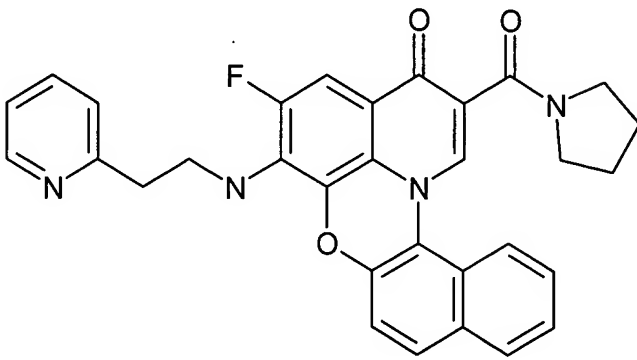
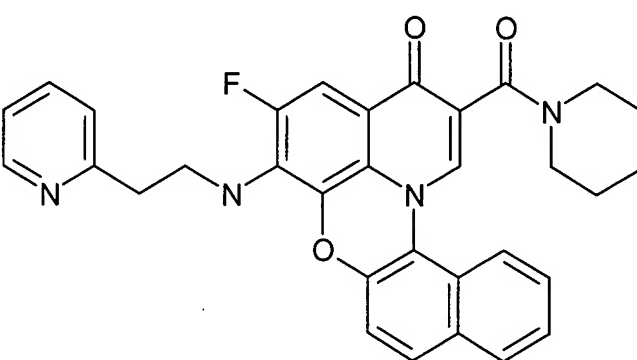
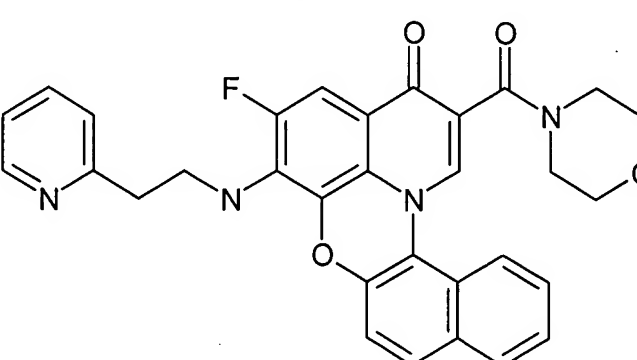
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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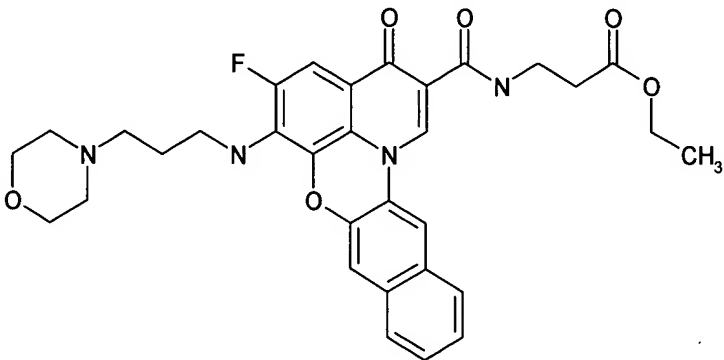
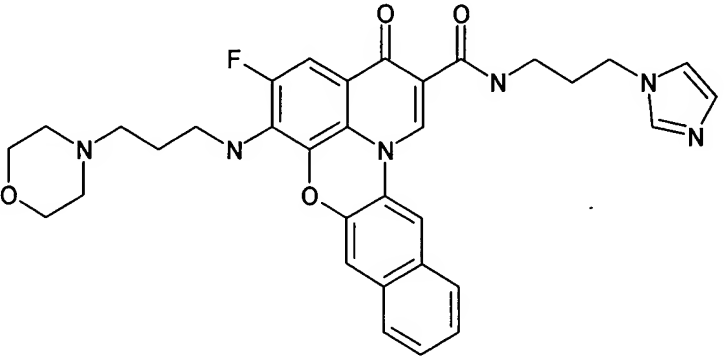
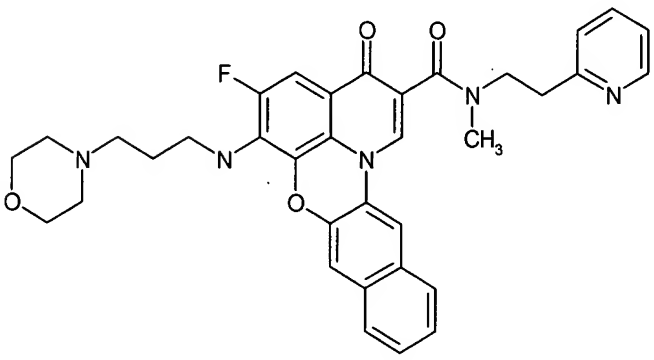
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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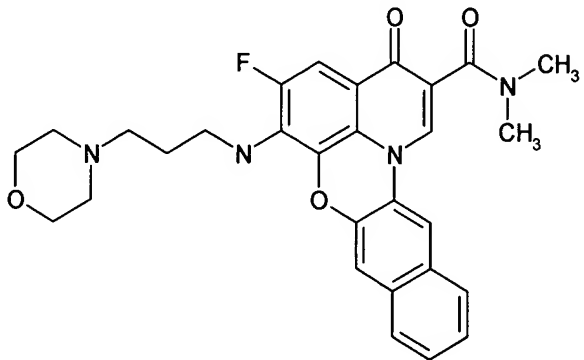
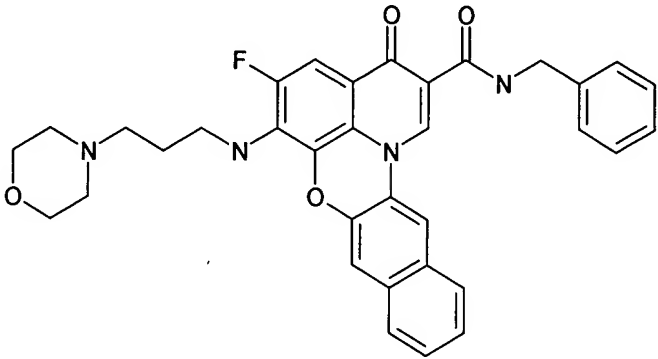
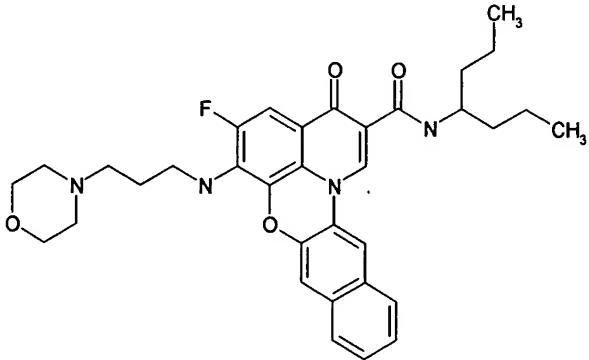
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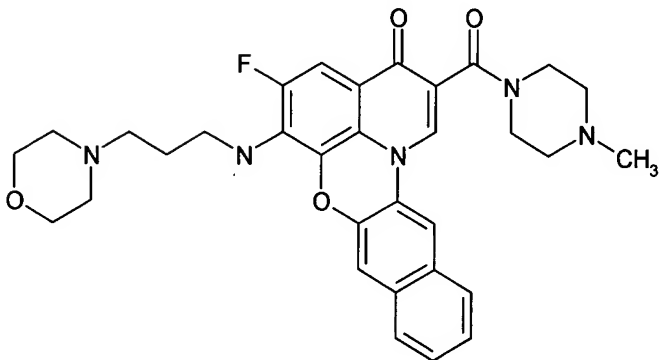
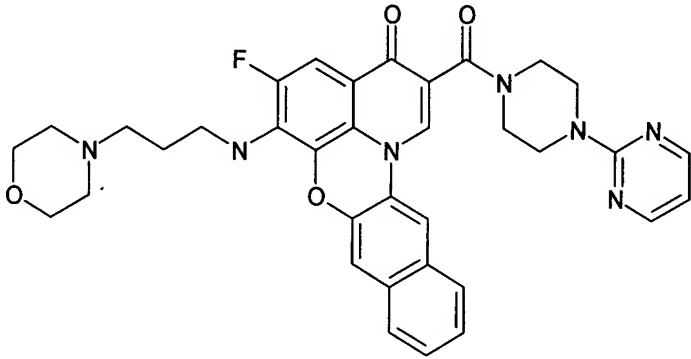
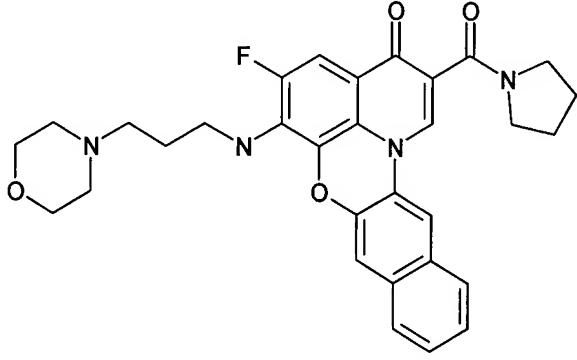


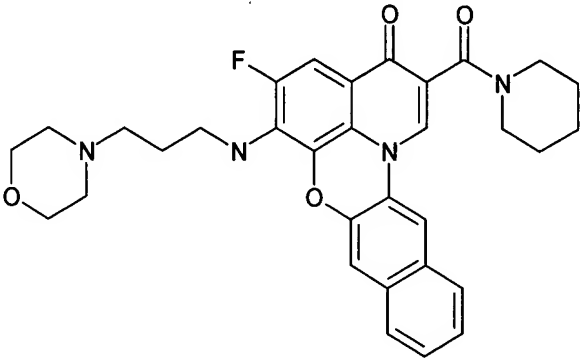
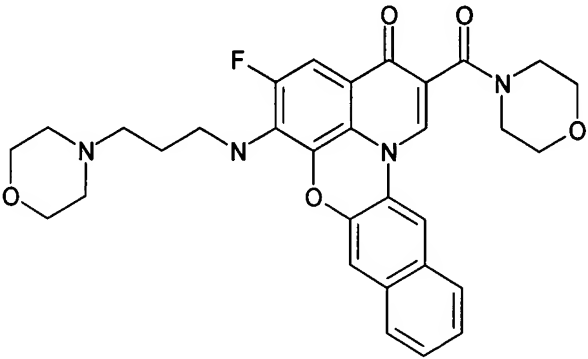
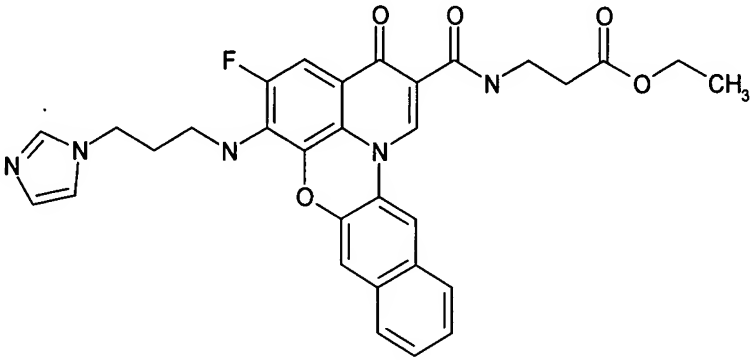
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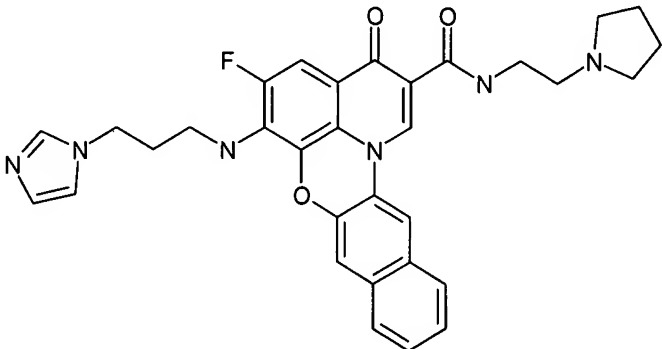
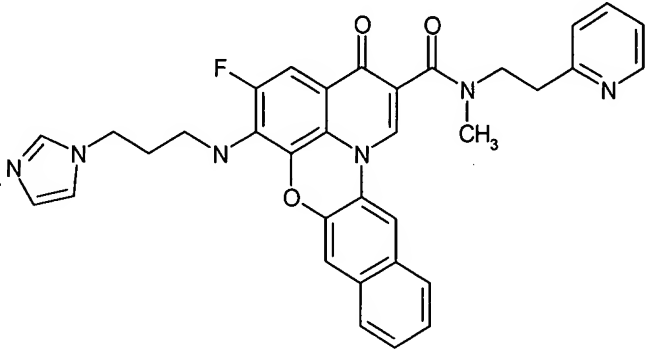
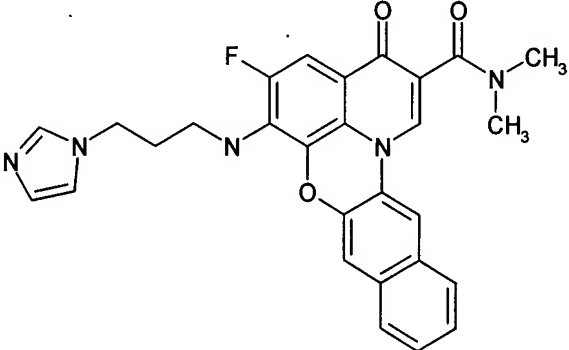
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
721			
722			
723			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
724			
725			
726			

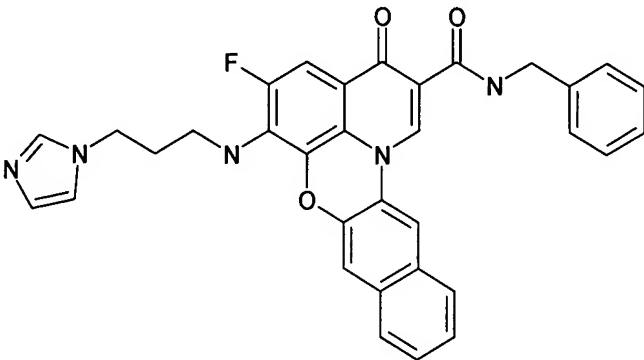
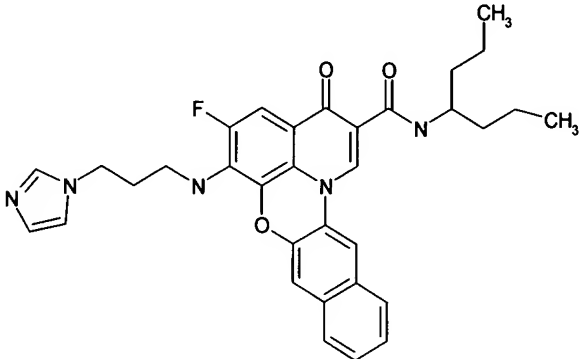
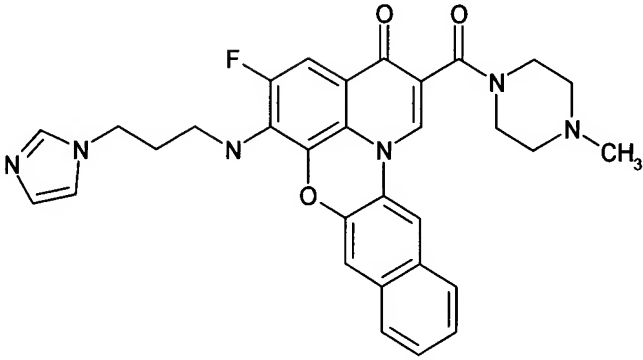
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
730			
731			
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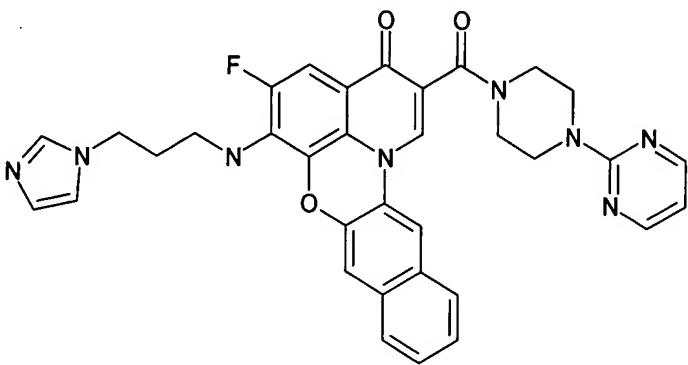
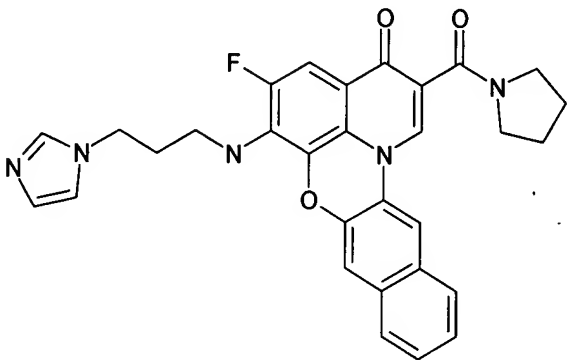
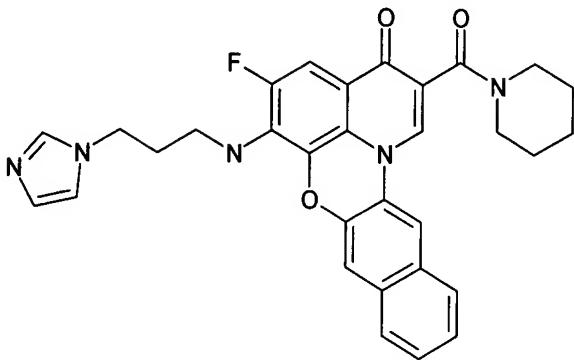
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272  
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152

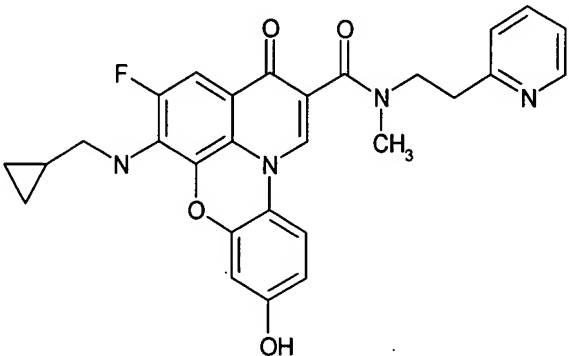
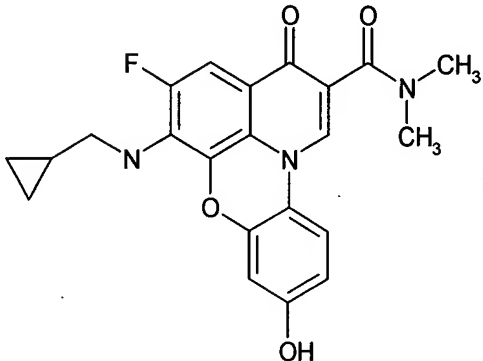
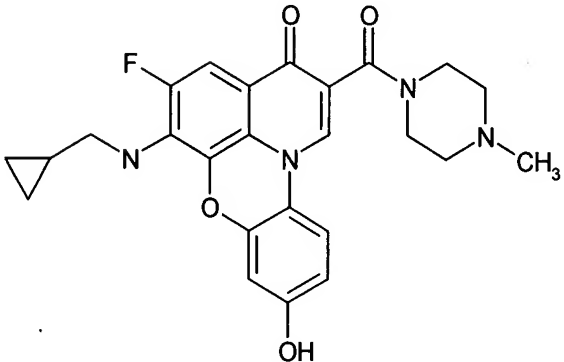
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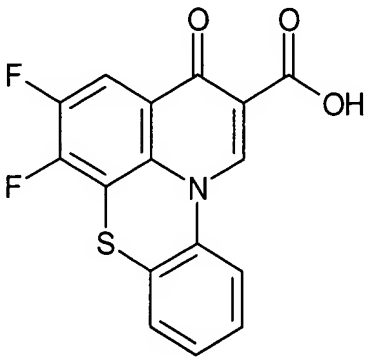
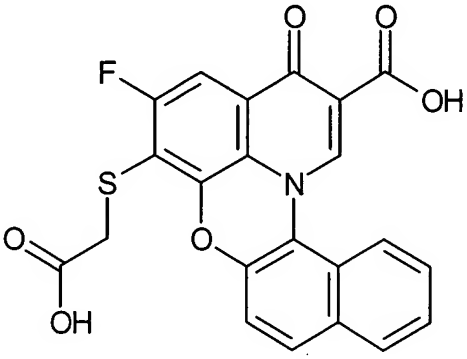
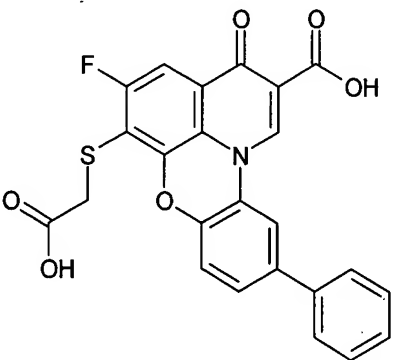
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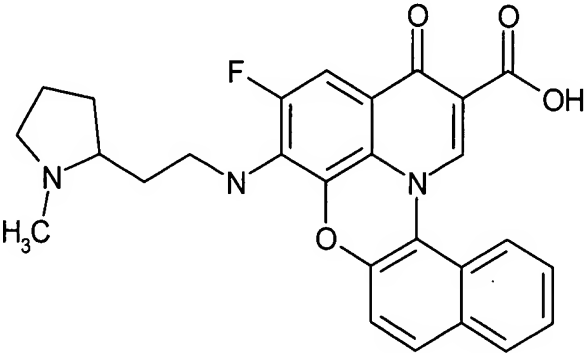
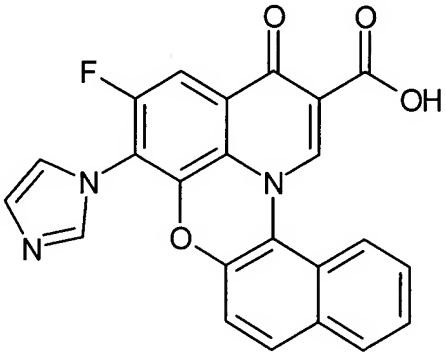
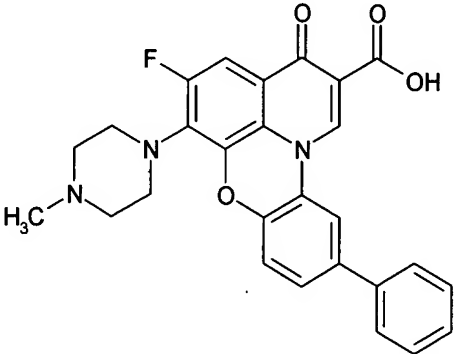
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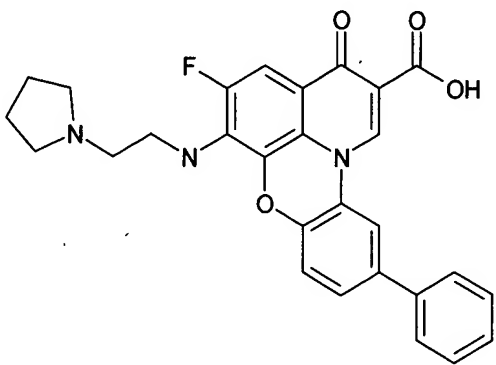
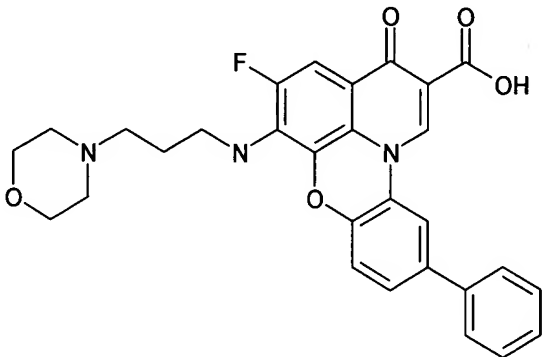
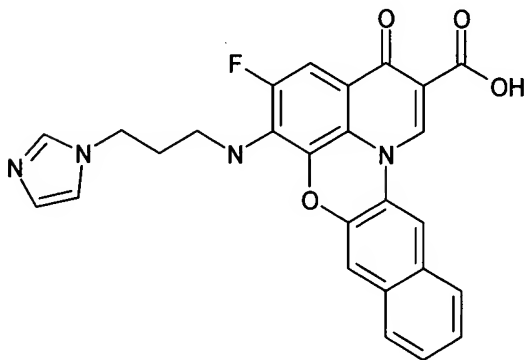
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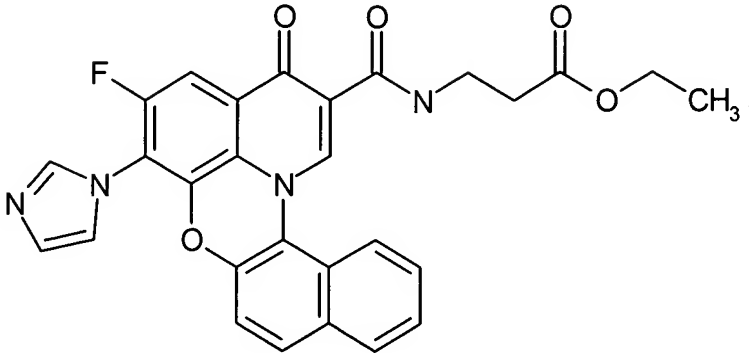
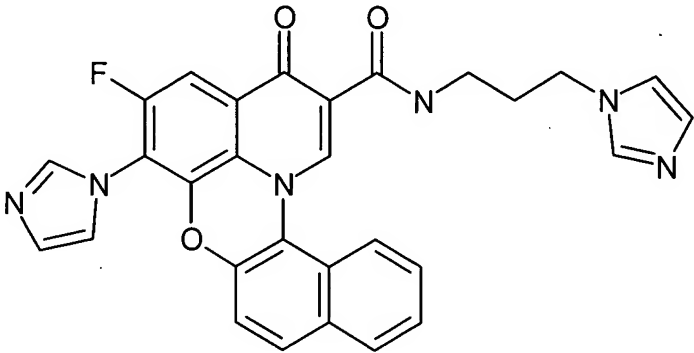
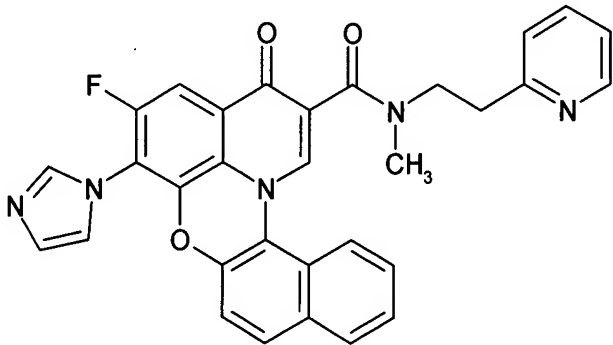
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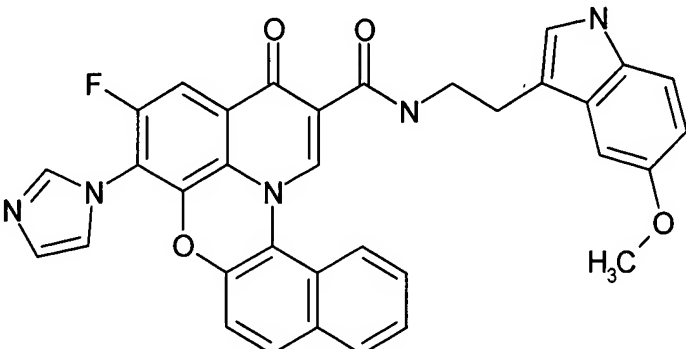
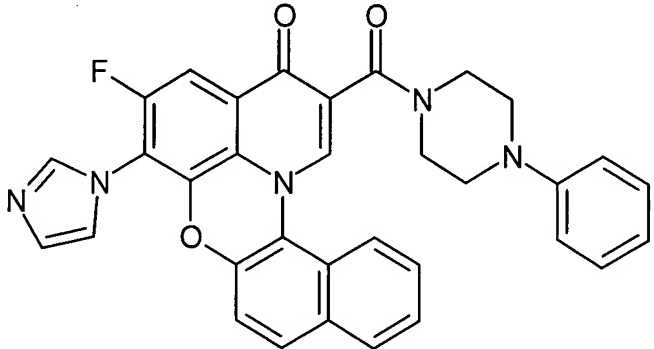
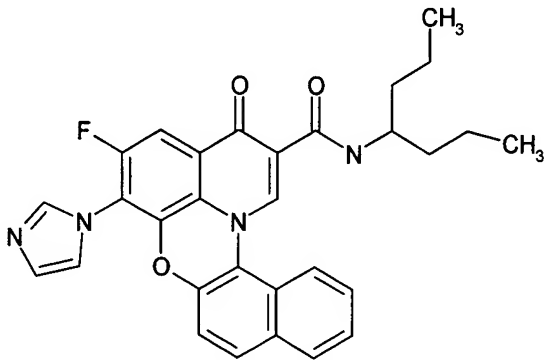
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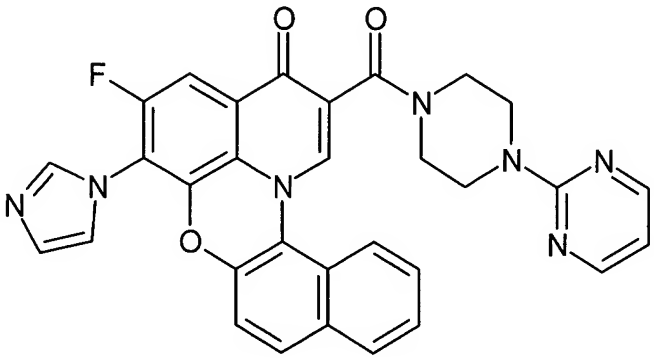
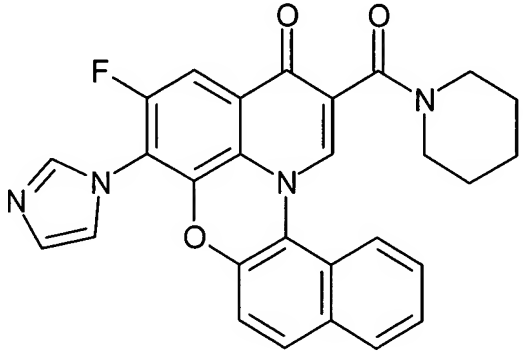
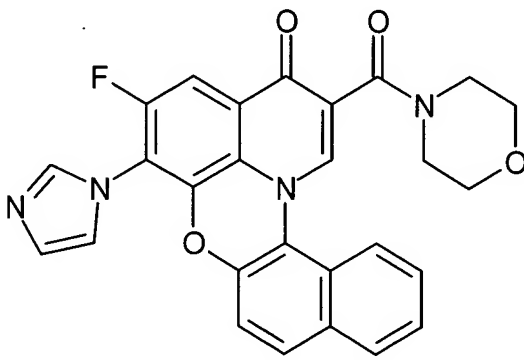
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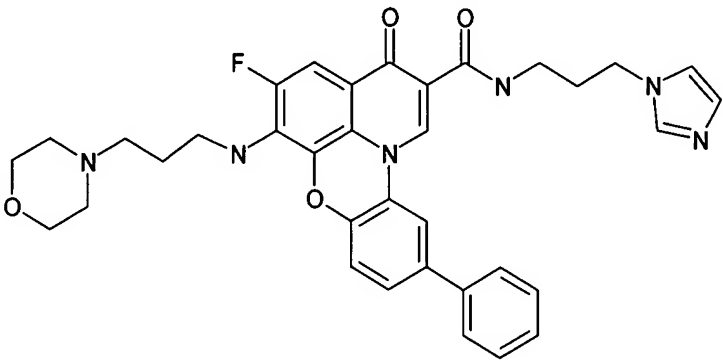
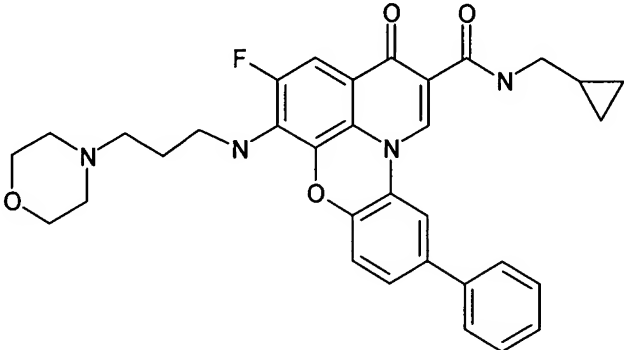
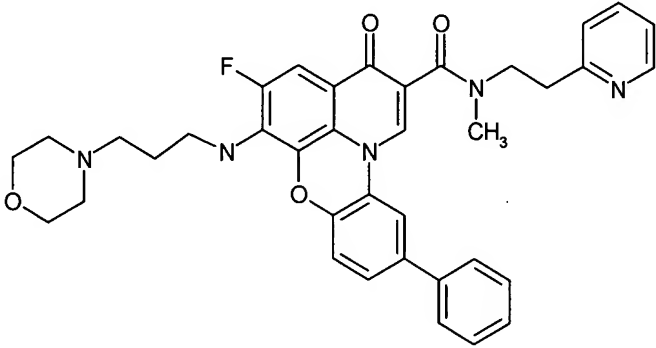


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764			
765			

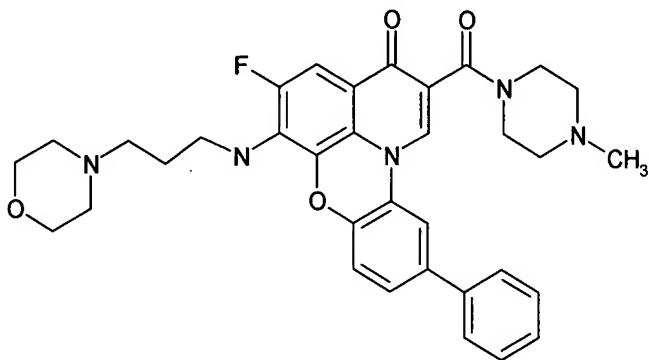
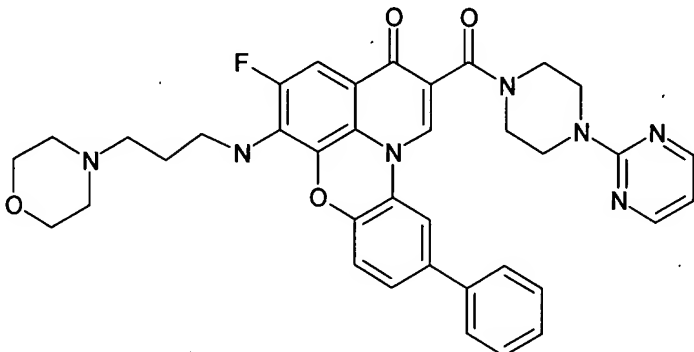
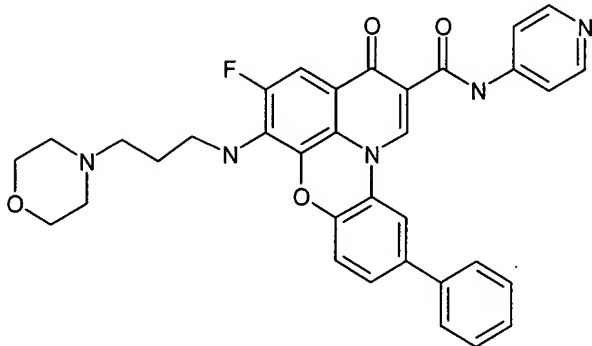
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767			
768			

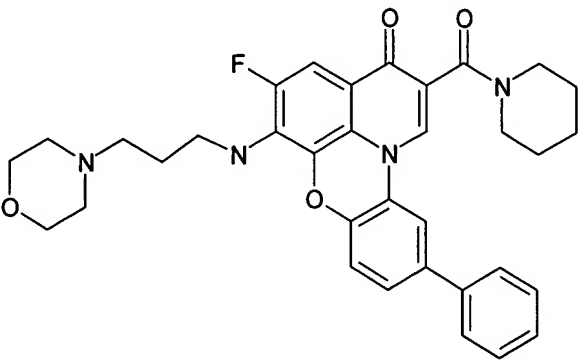
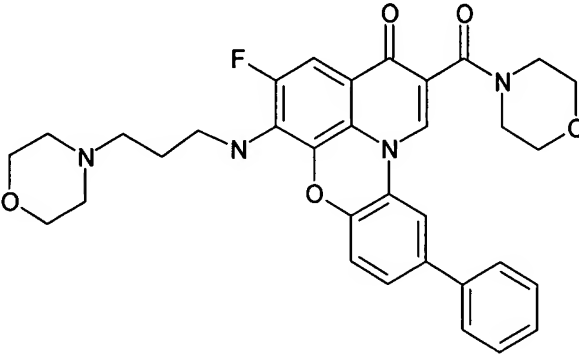
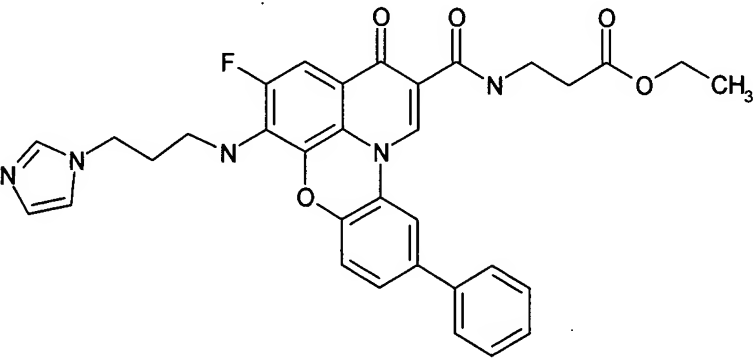
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
772			
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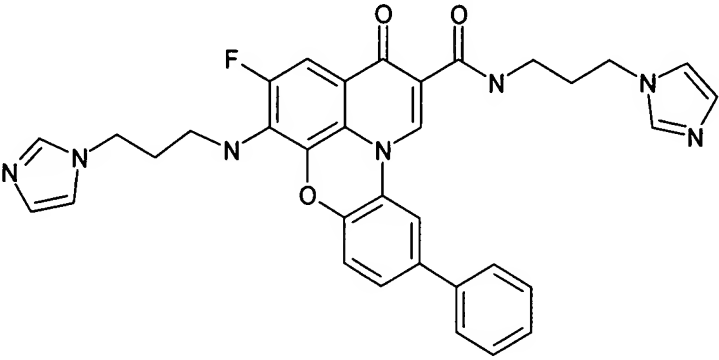
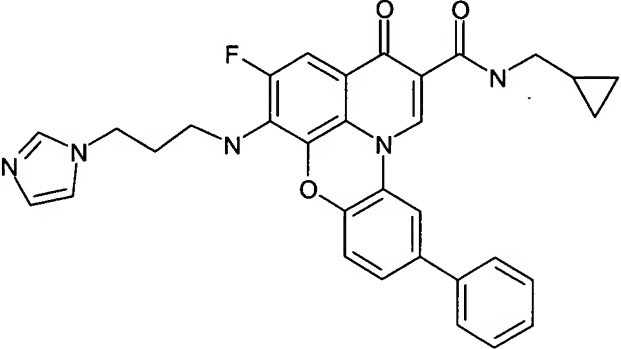
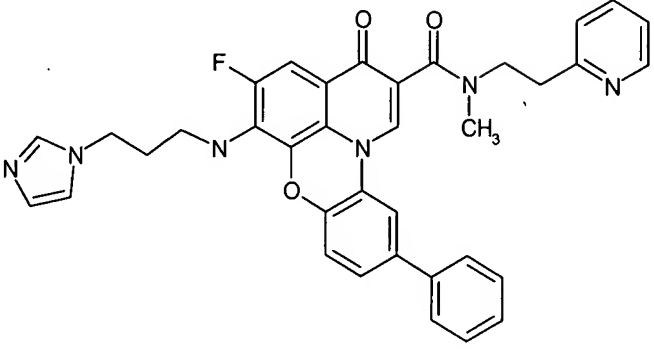
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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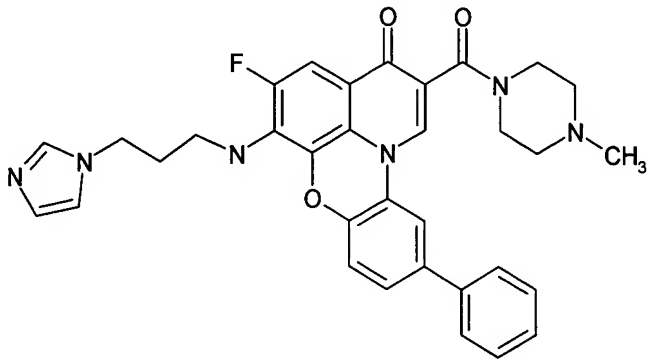
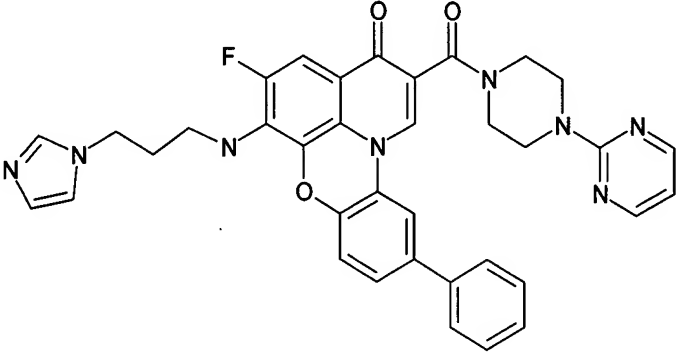
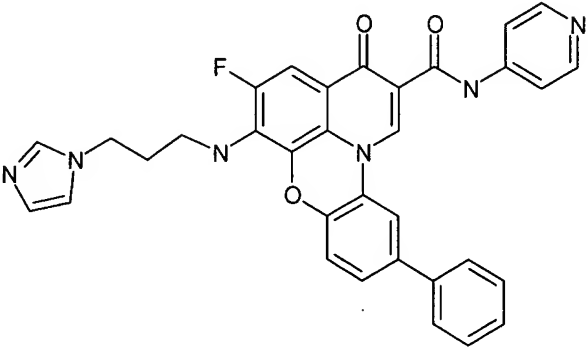
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783			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
784			
785			
786			



	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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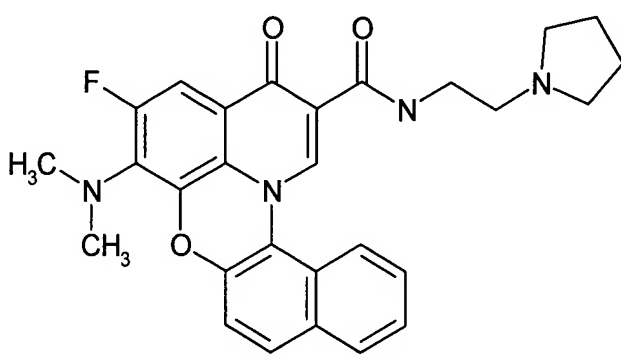
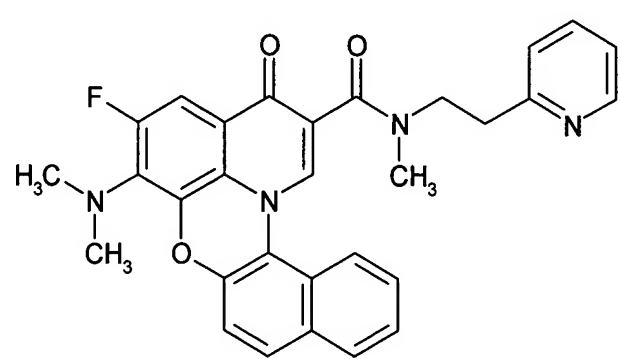
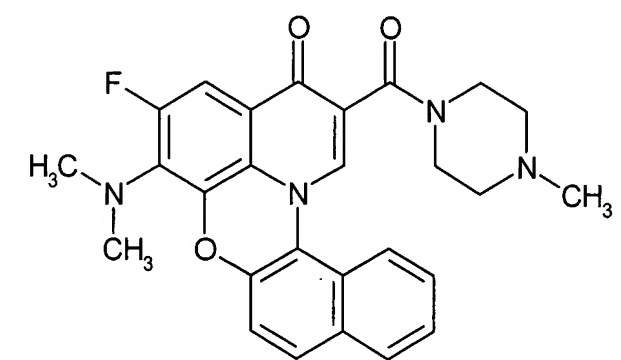
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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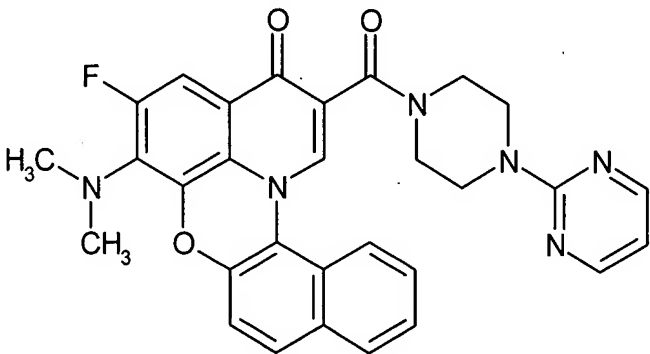
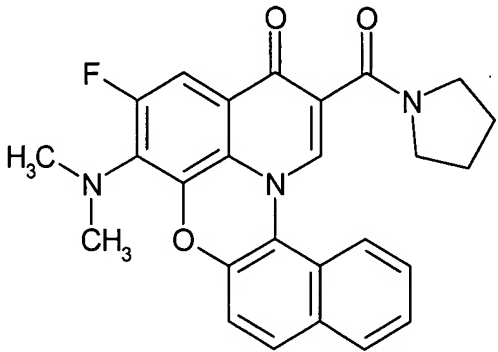
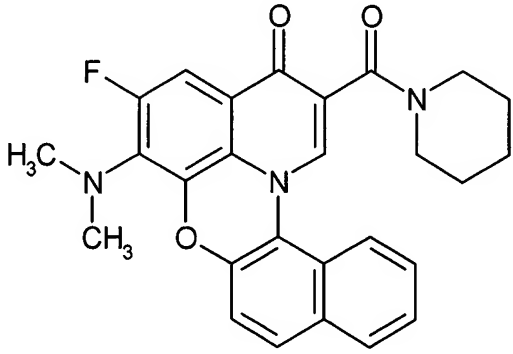
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801			

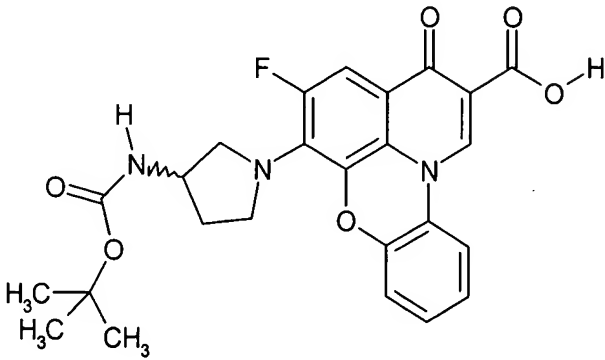
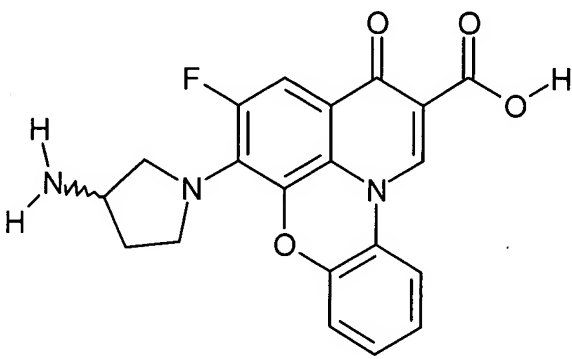
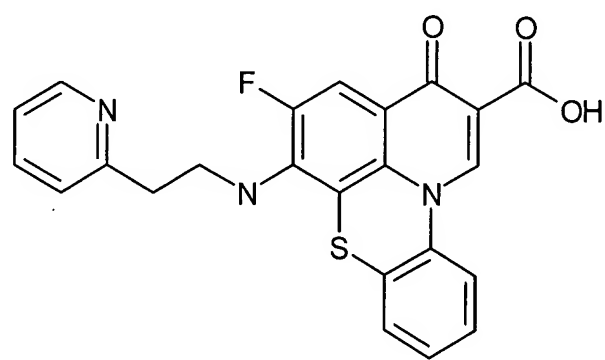
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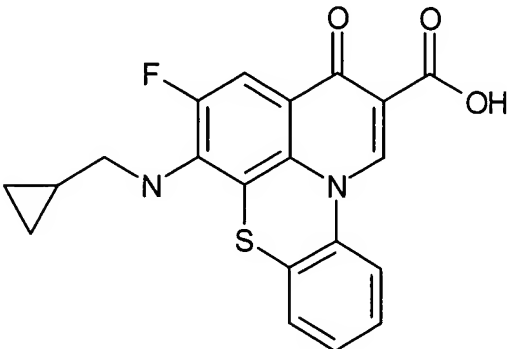
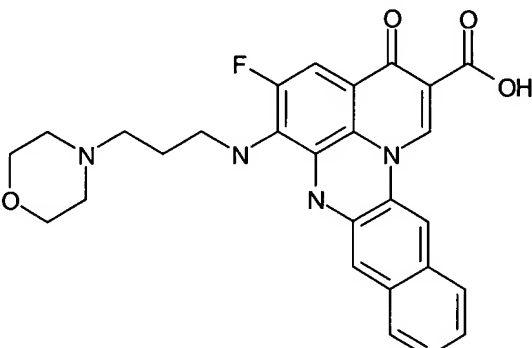
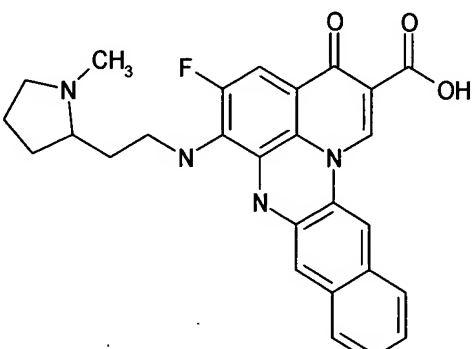
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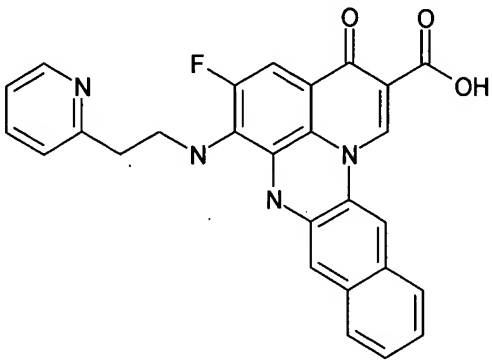
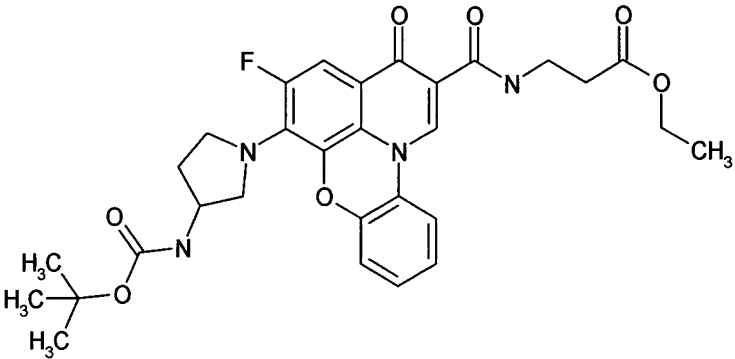
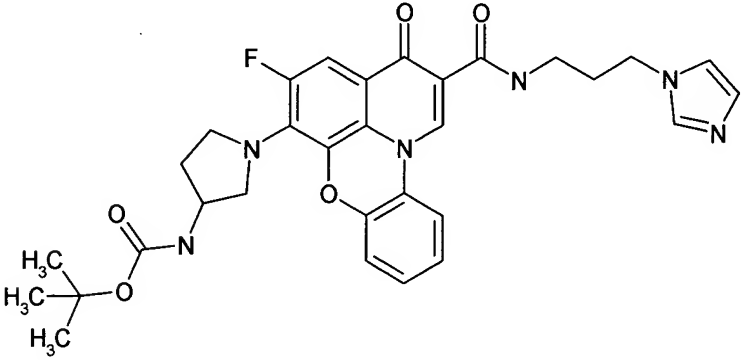
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809			
810			



	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
811			
812			
813			

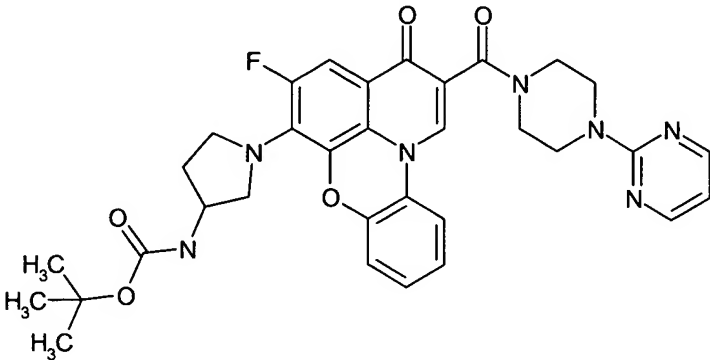
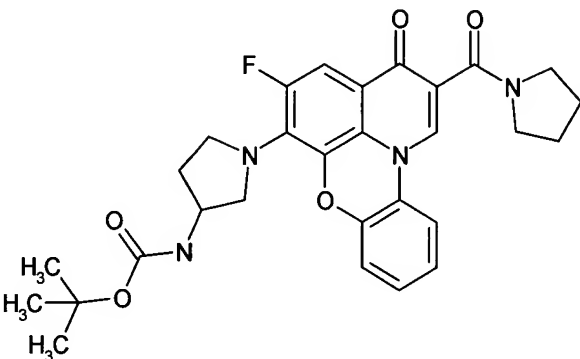
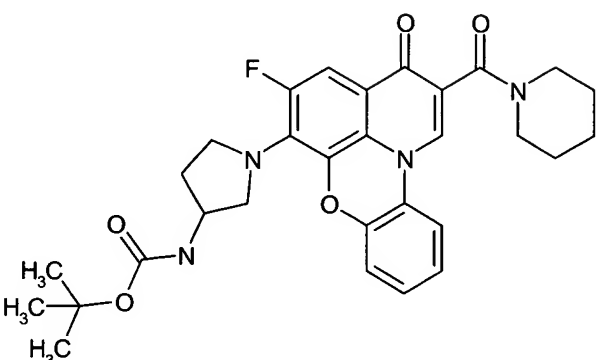
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814			
815			
816			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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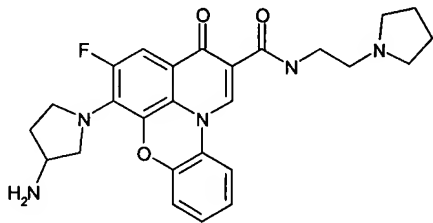
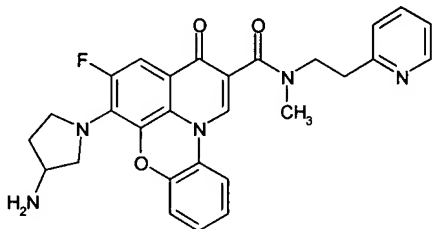
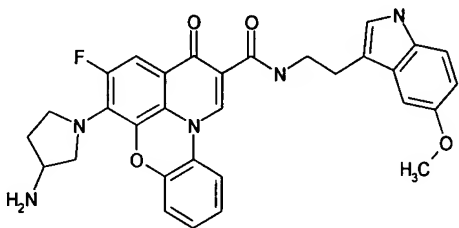
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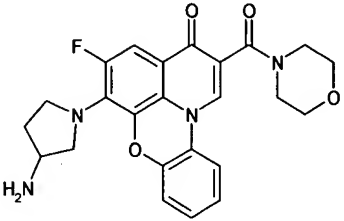
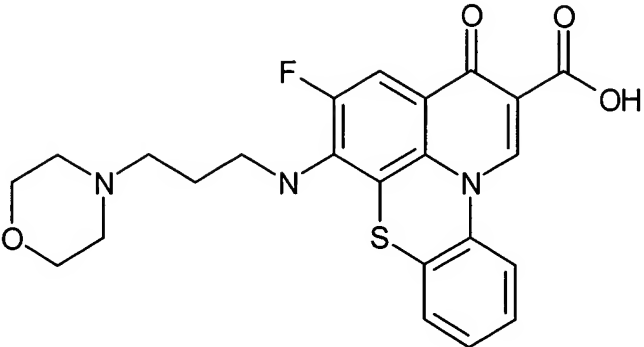
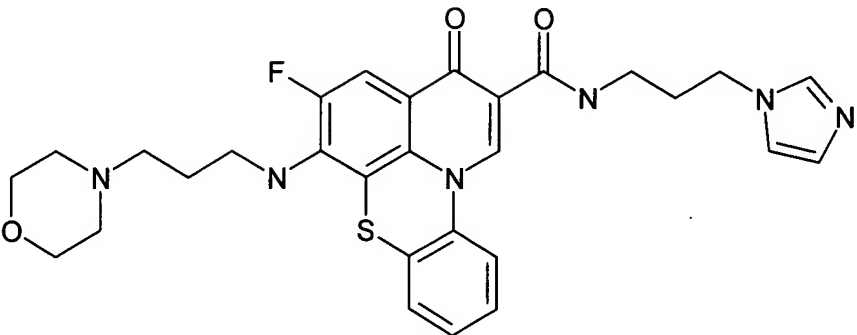
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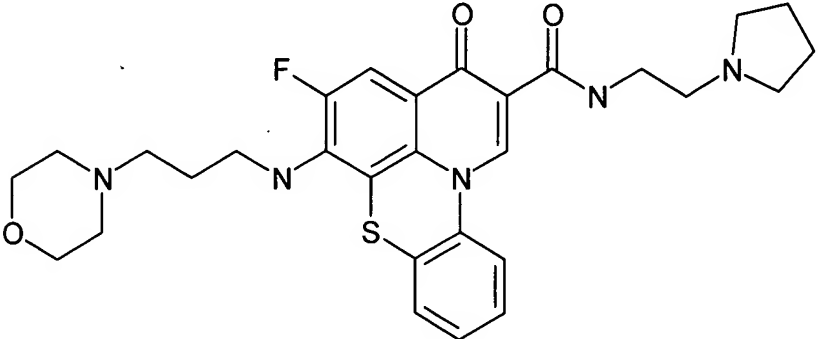
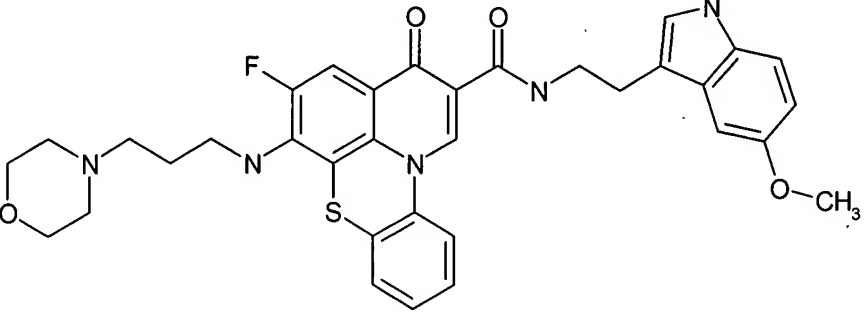
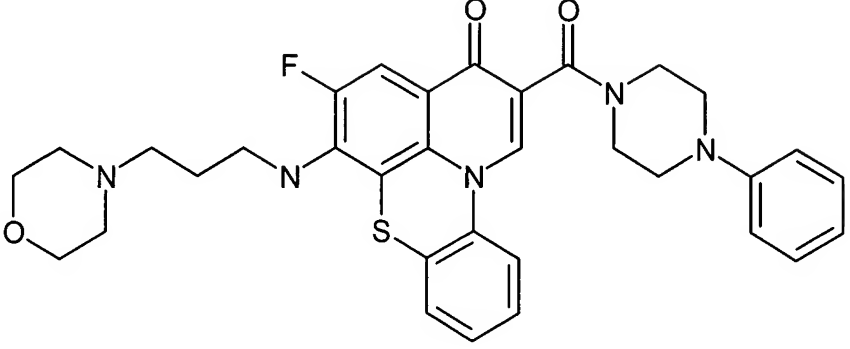


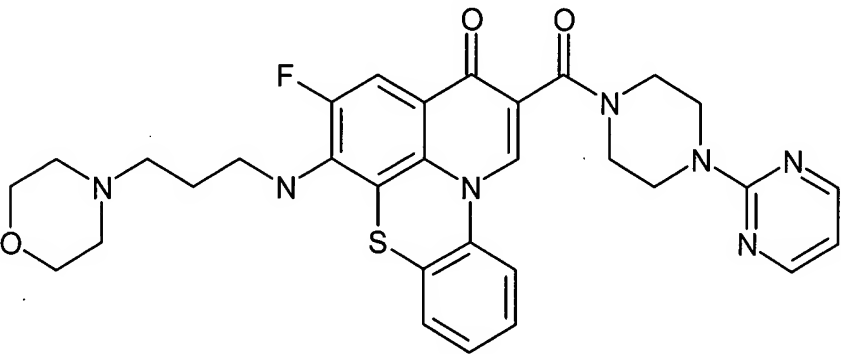
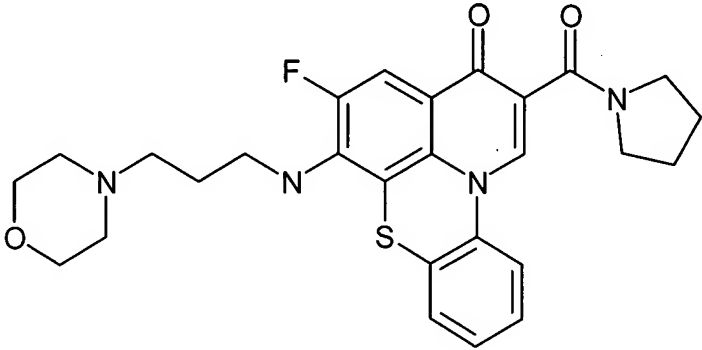
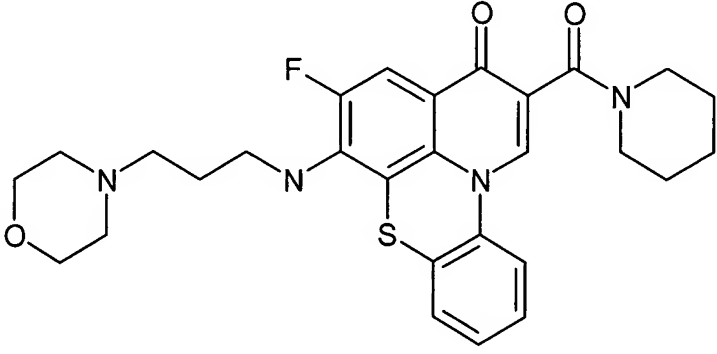
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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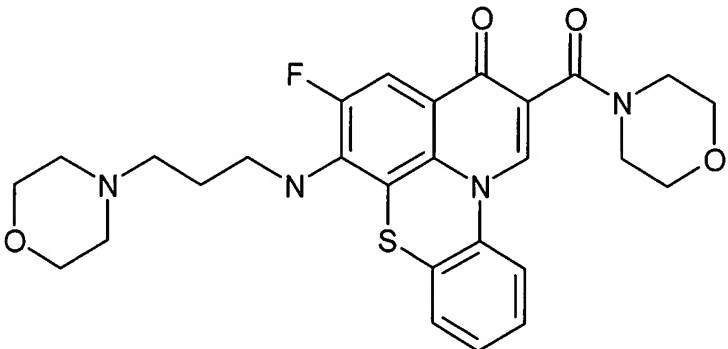
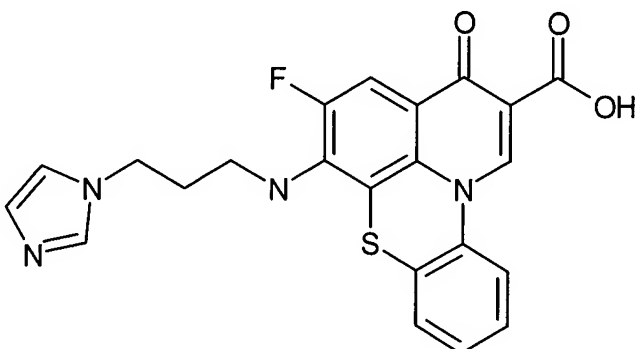
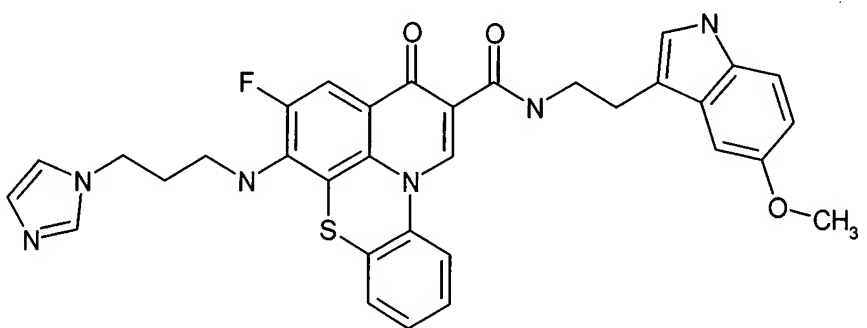
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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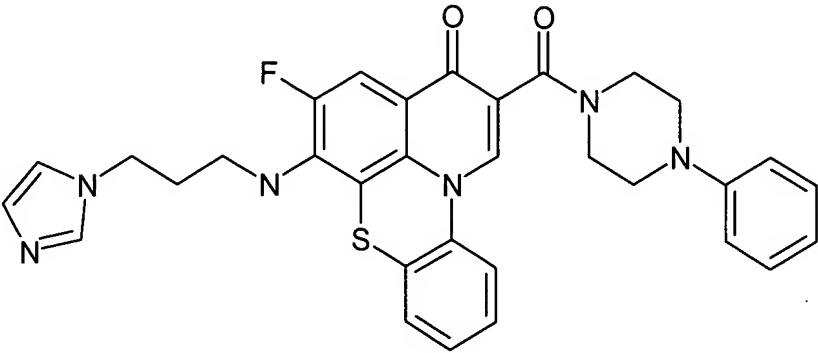
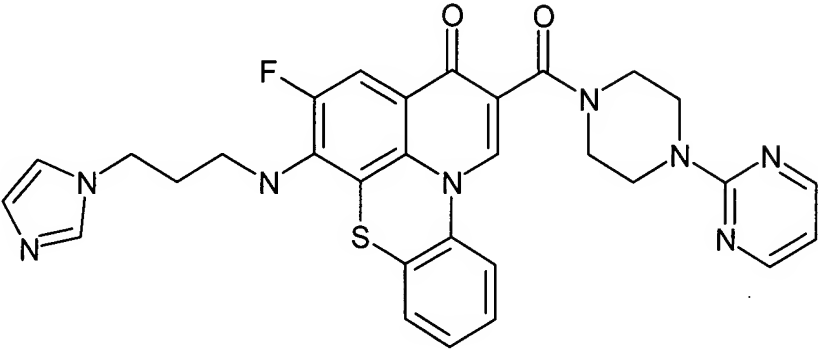
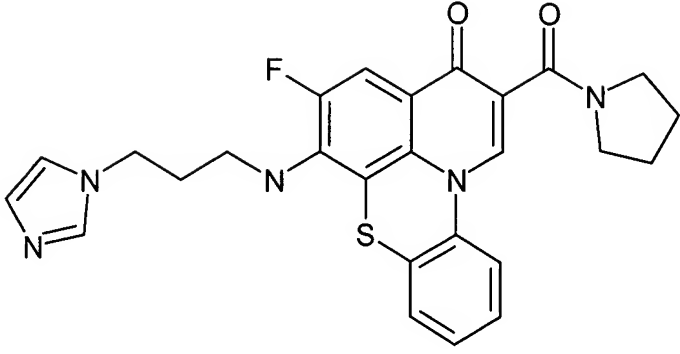
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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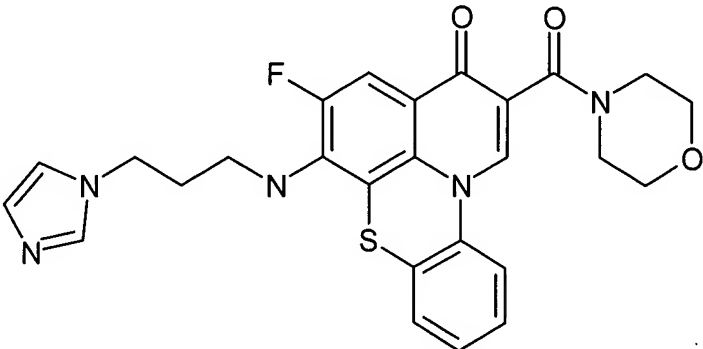
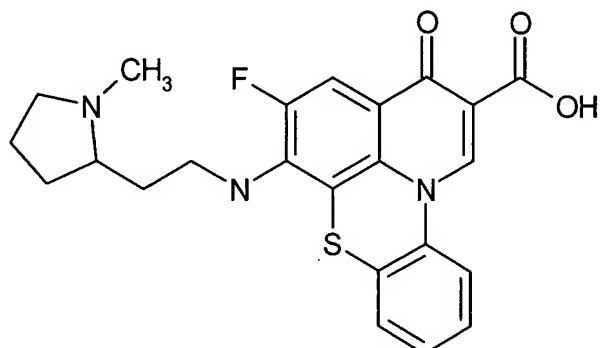
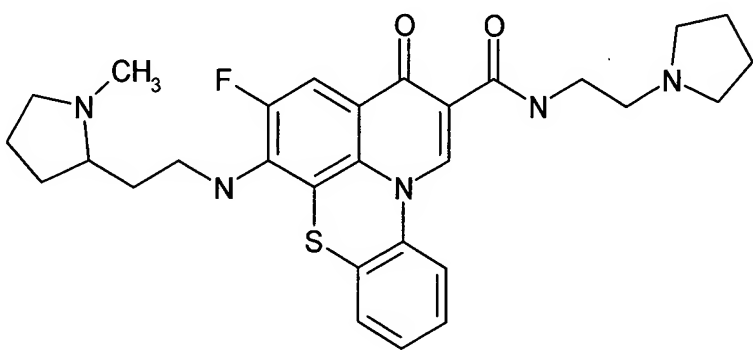
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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852			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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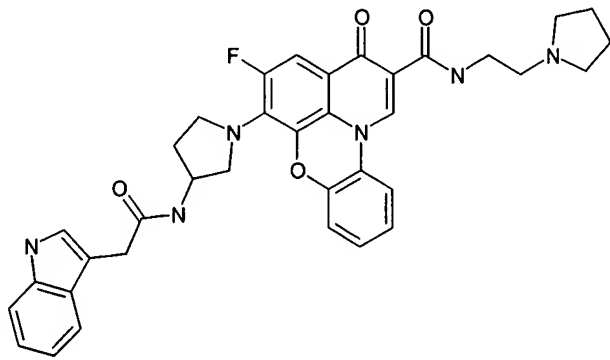
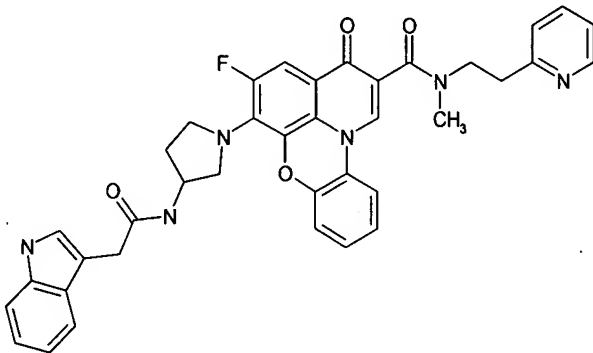
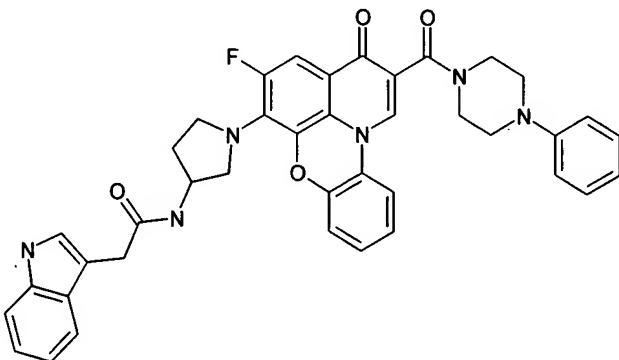
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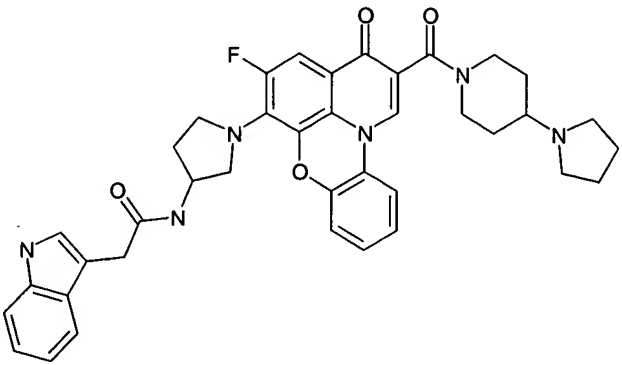
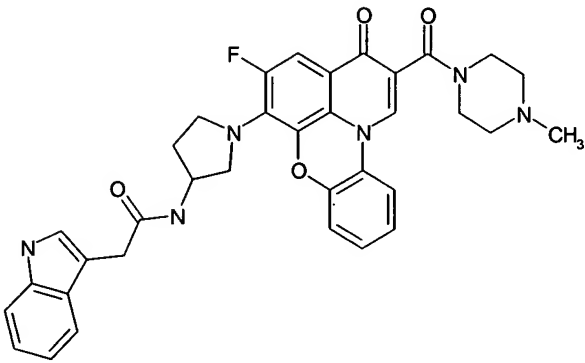
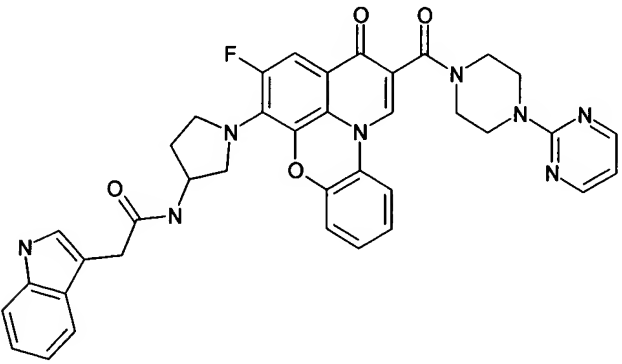


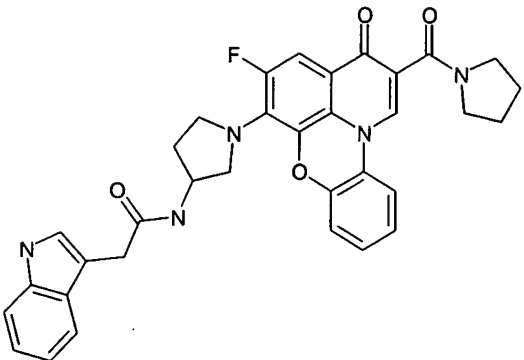
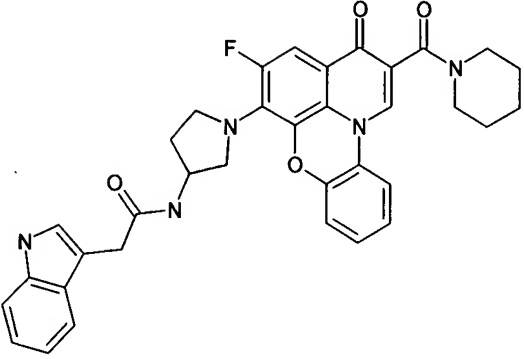
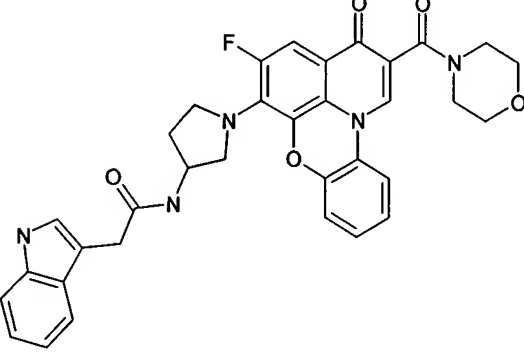
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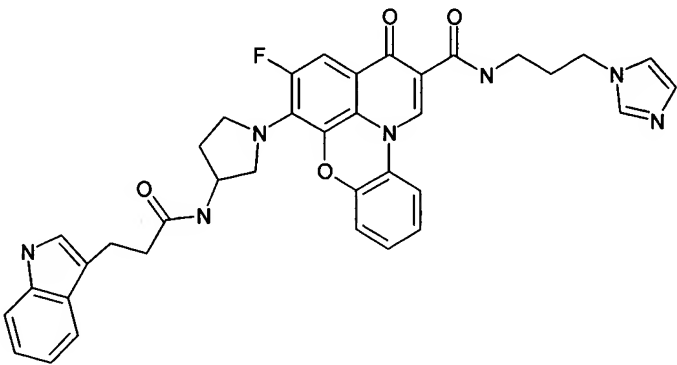
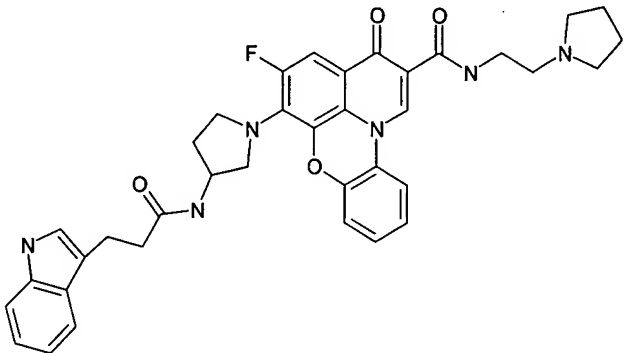
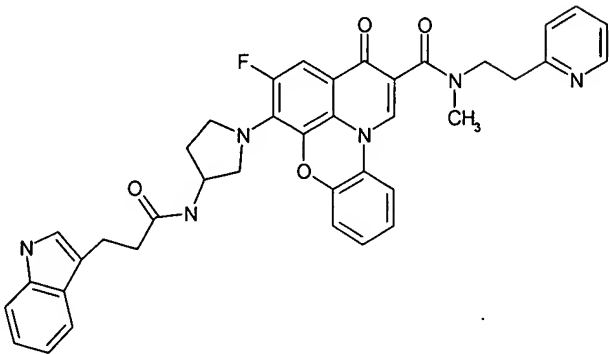
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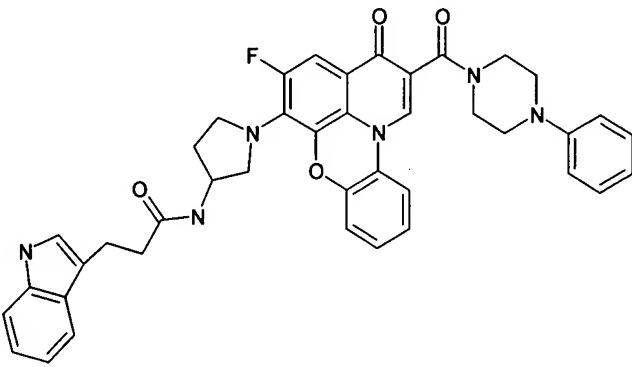
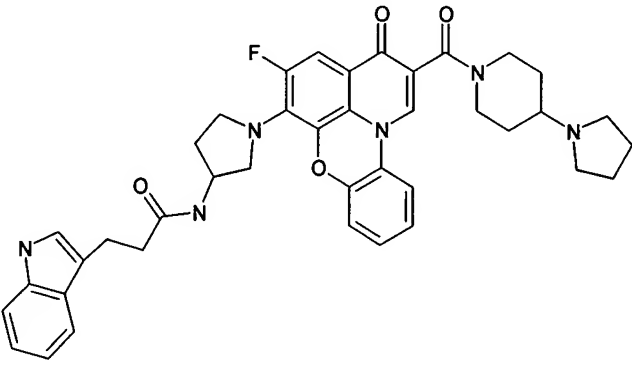
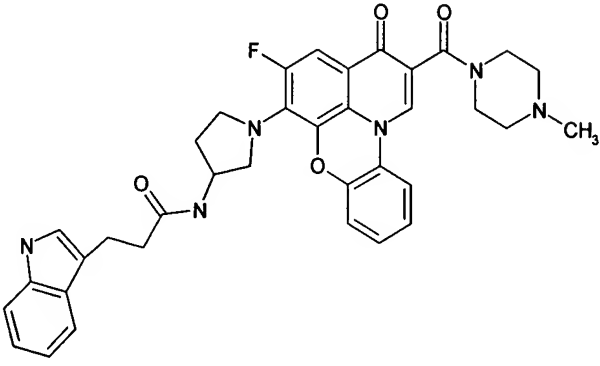
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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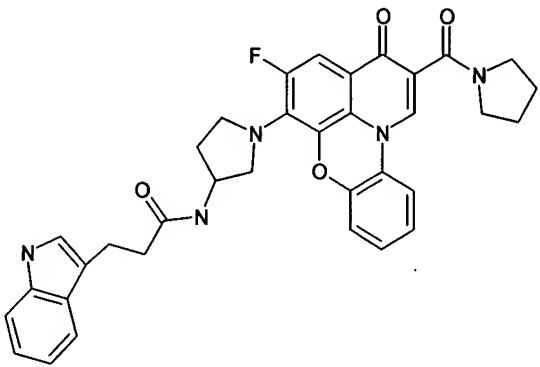
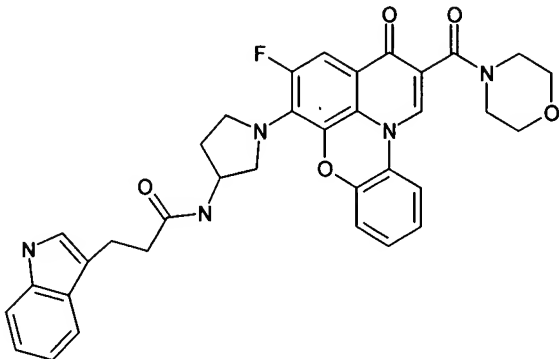
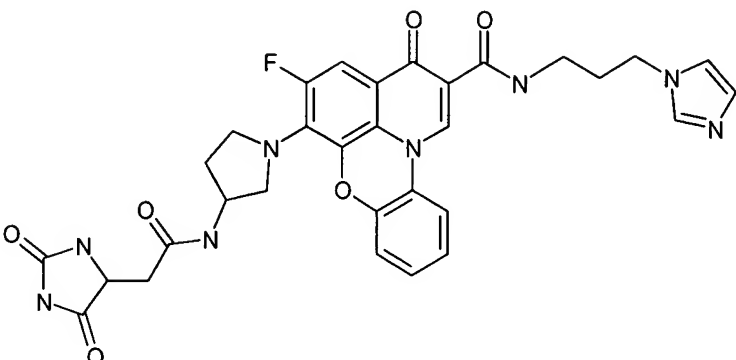
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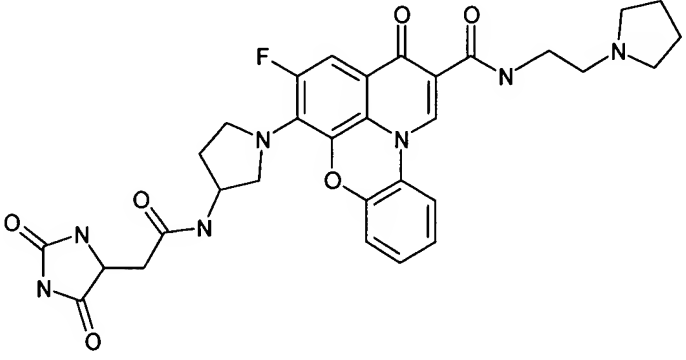
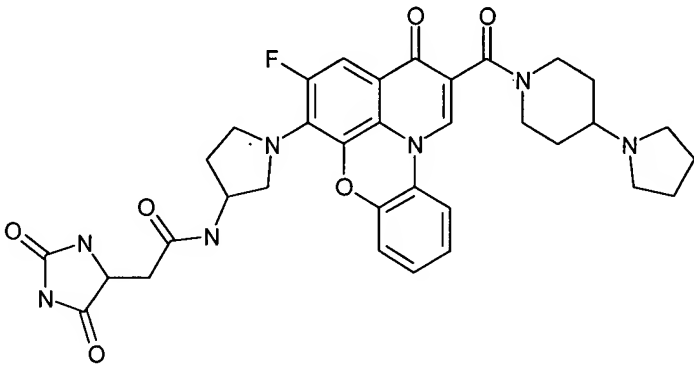
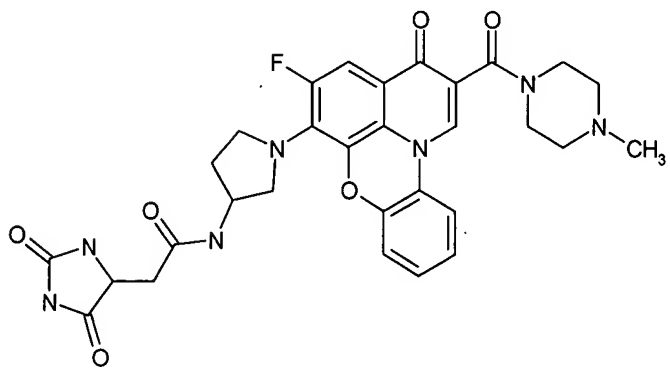
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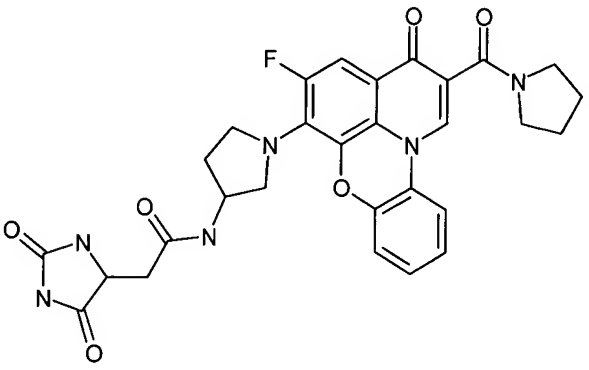
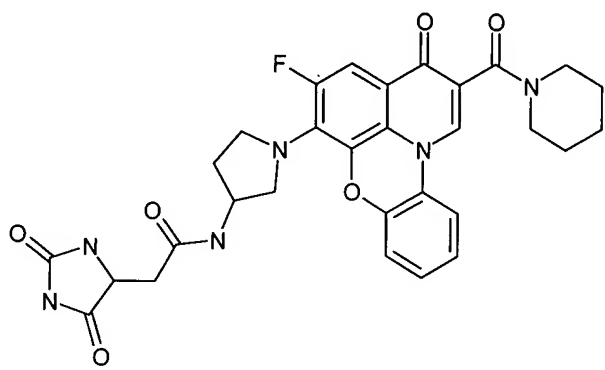
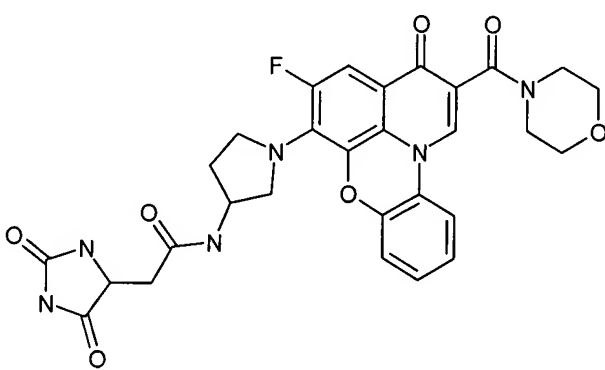
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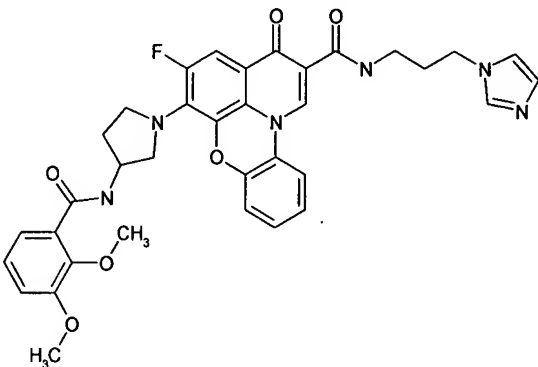
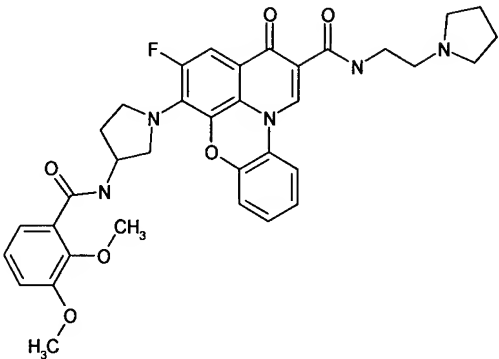
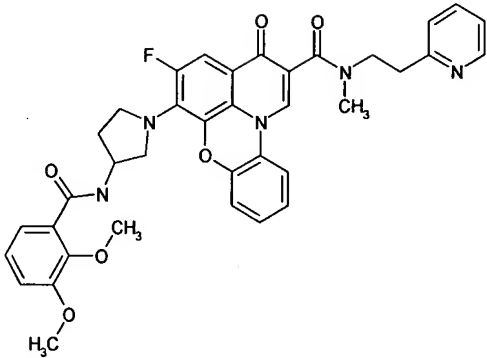
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882			



	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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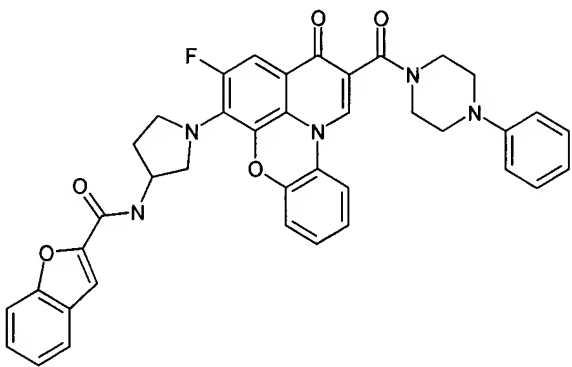
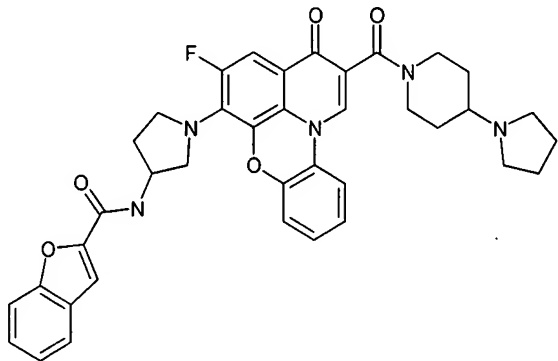
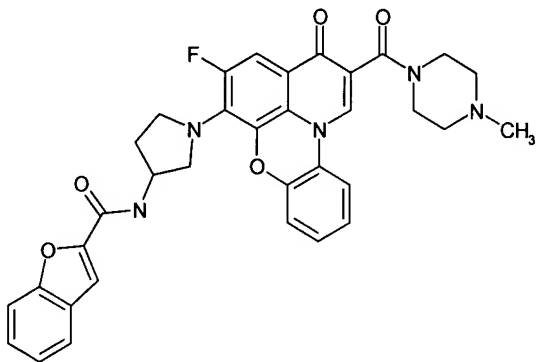
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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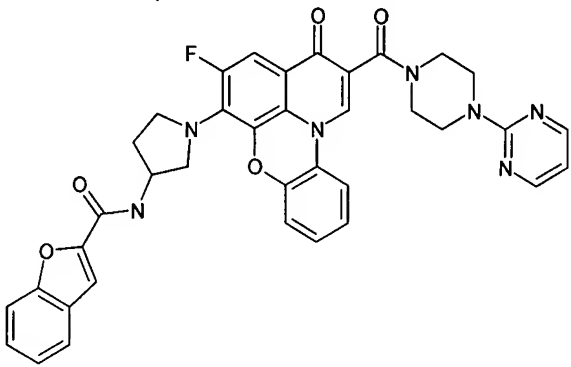
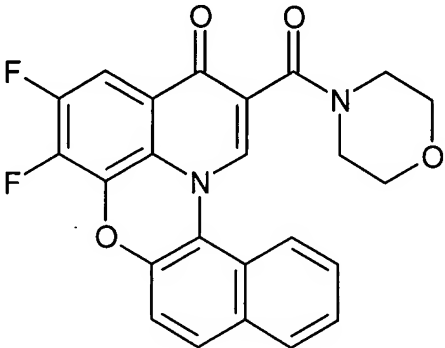
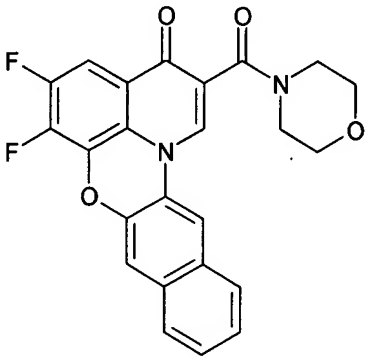
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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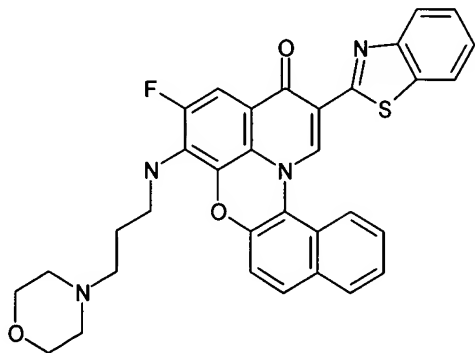
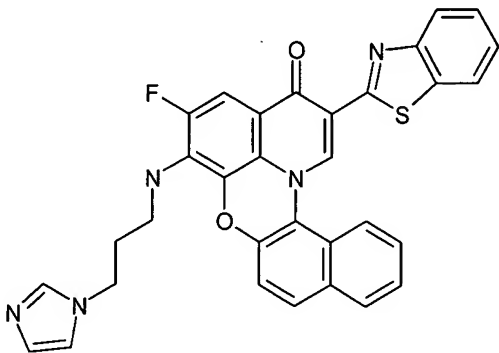
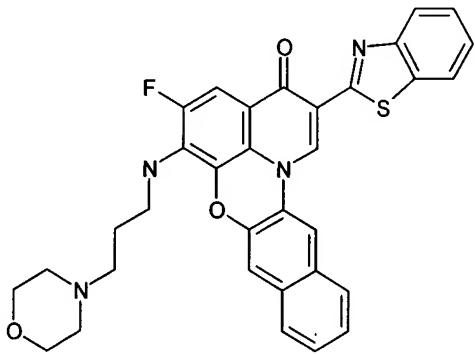
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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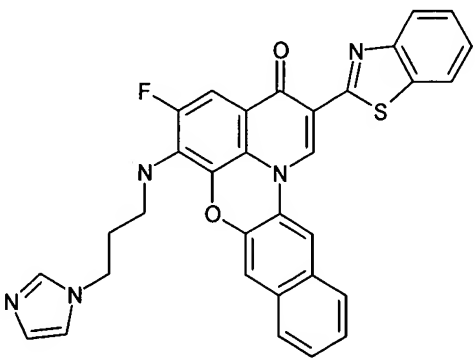
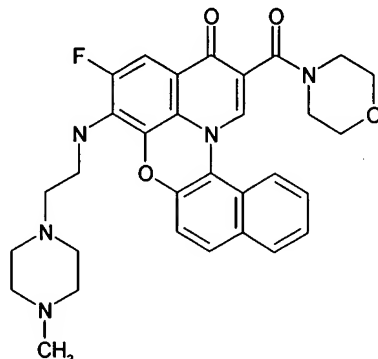
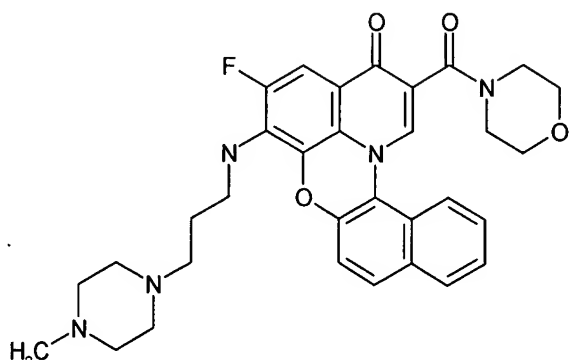
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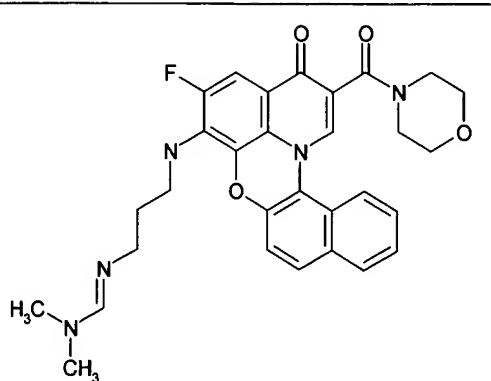
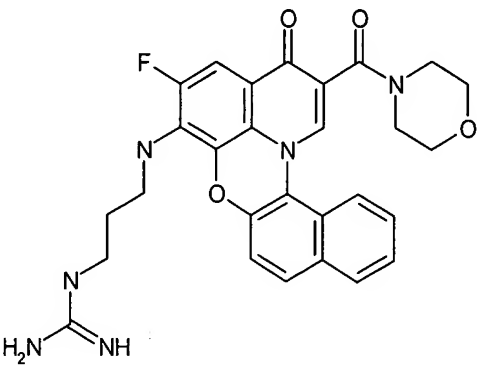
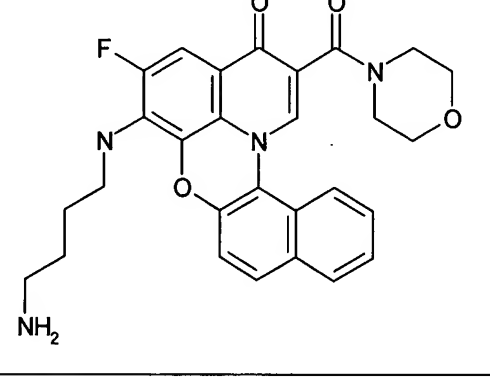


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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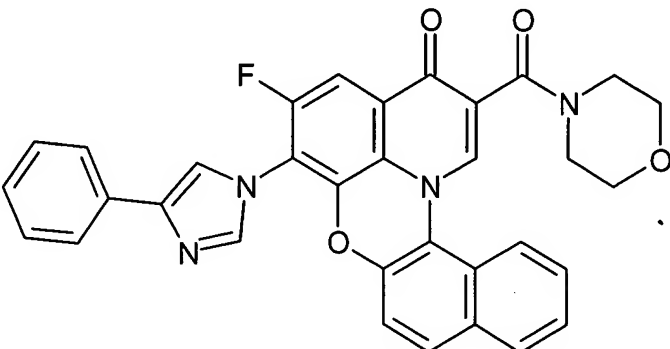
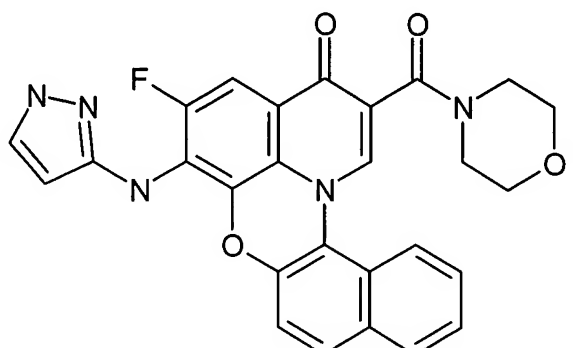
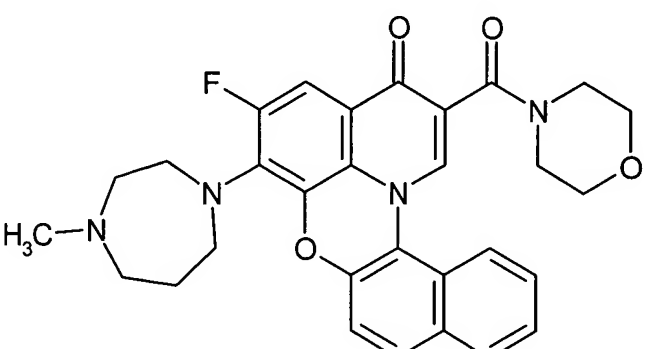
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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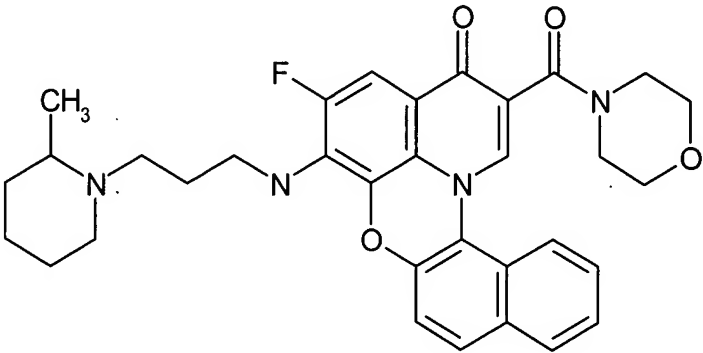
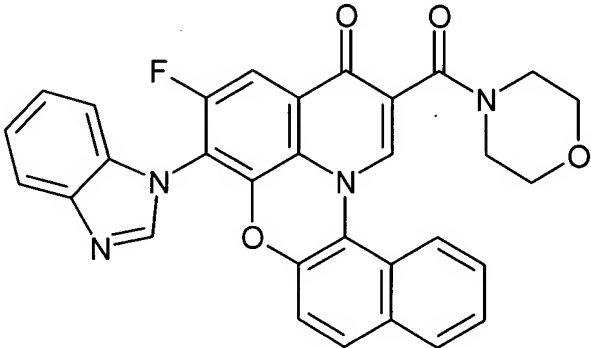
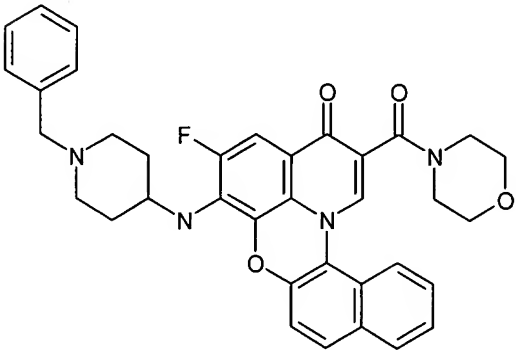
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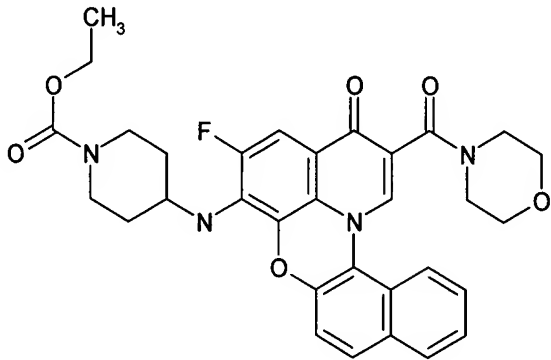
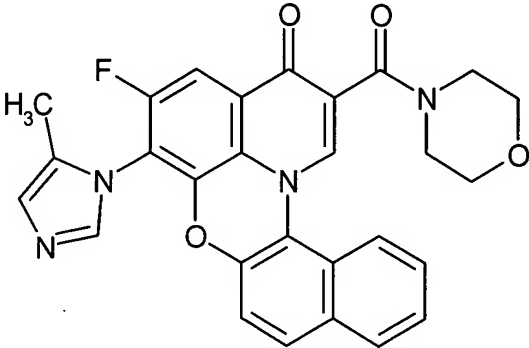
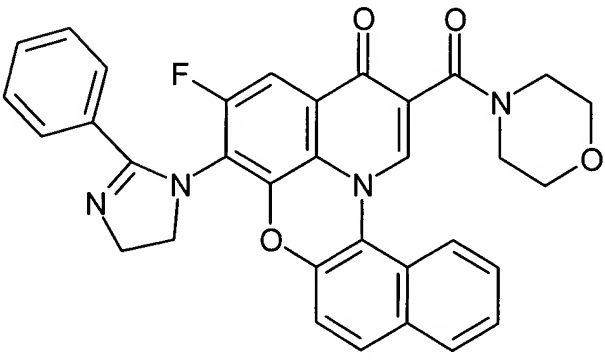
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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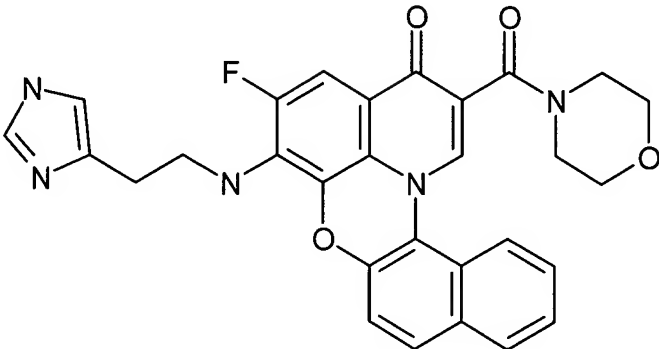
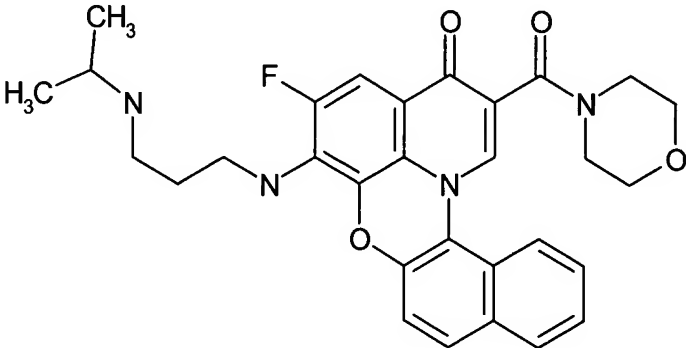
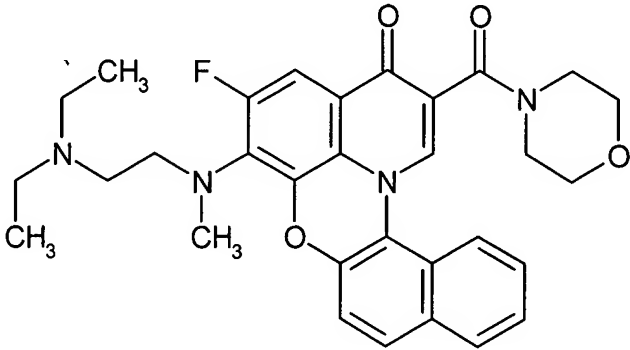
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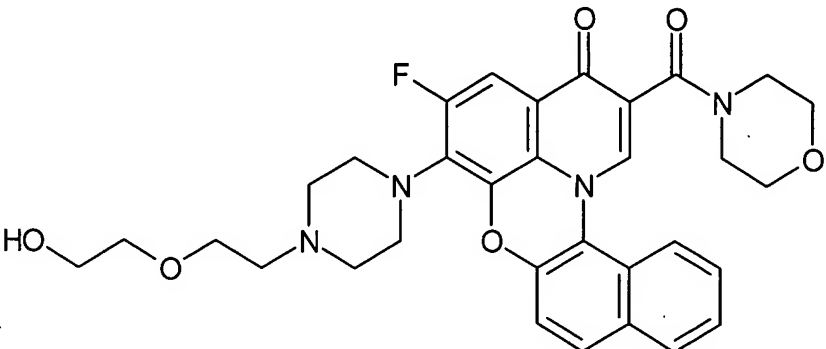
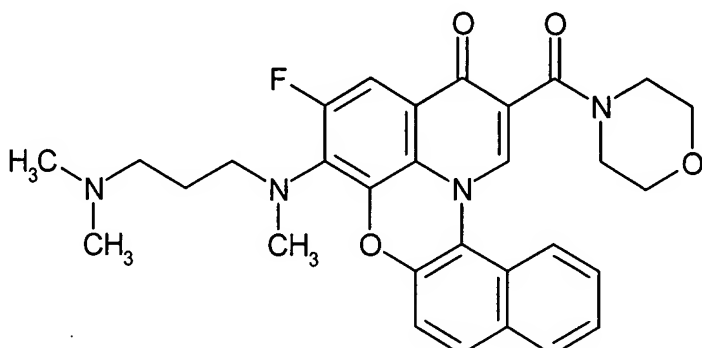
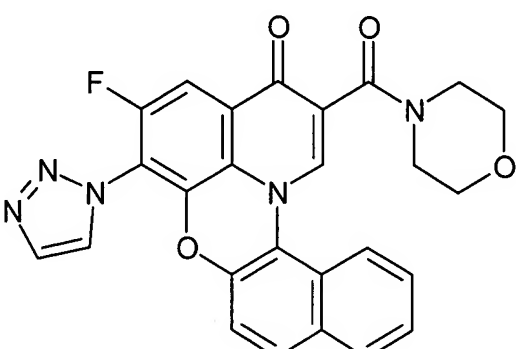


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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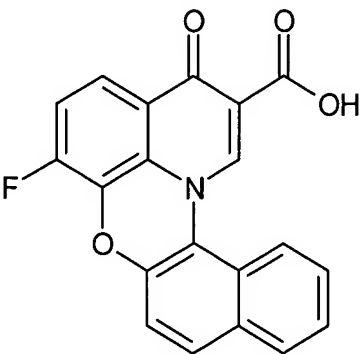
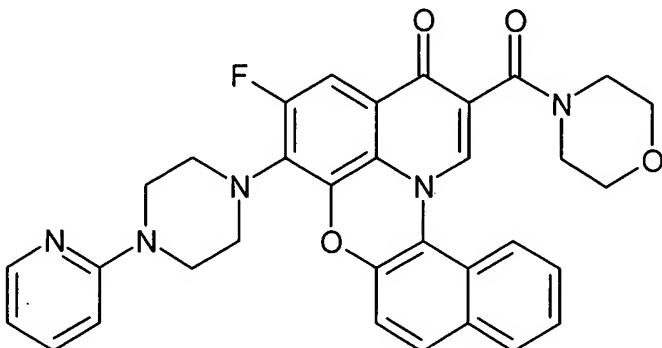
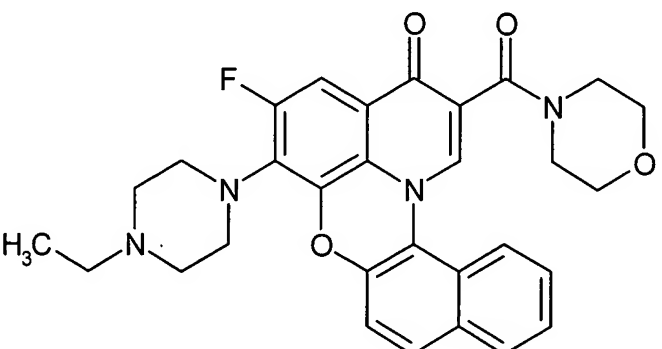
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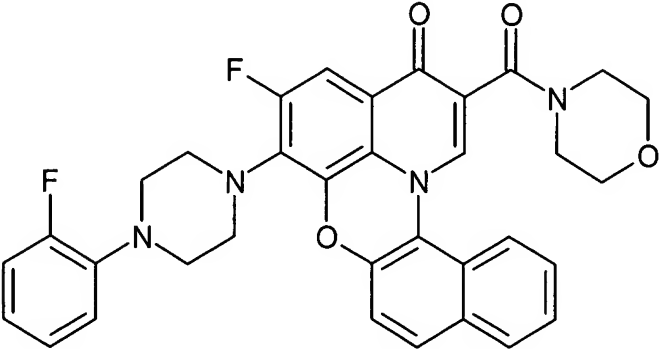
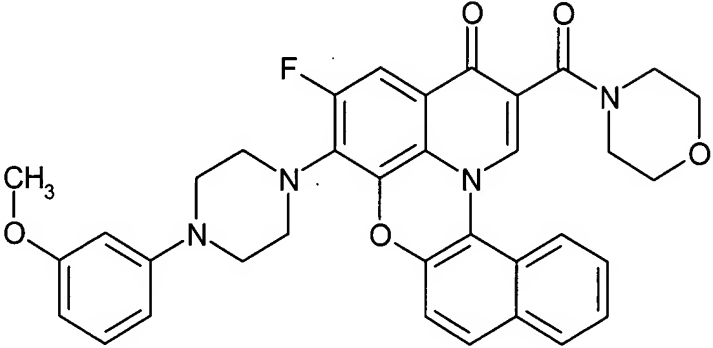
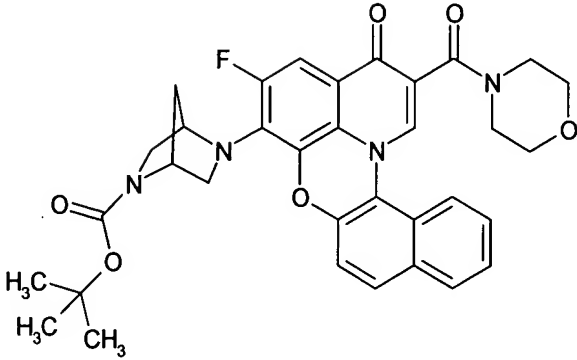
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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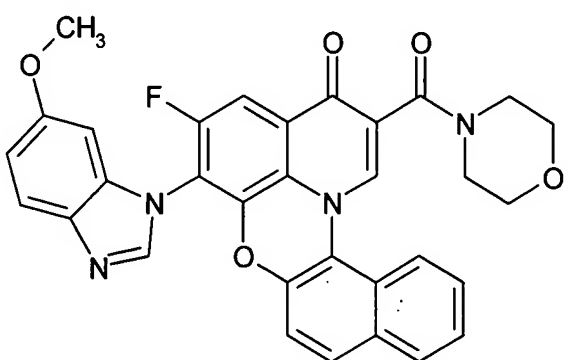
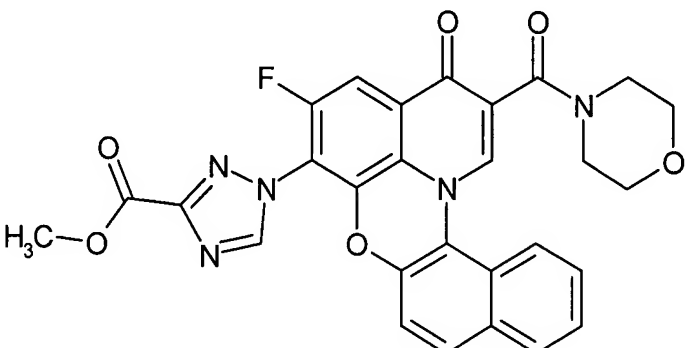
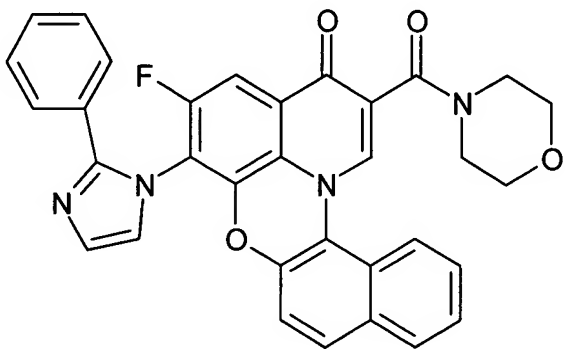
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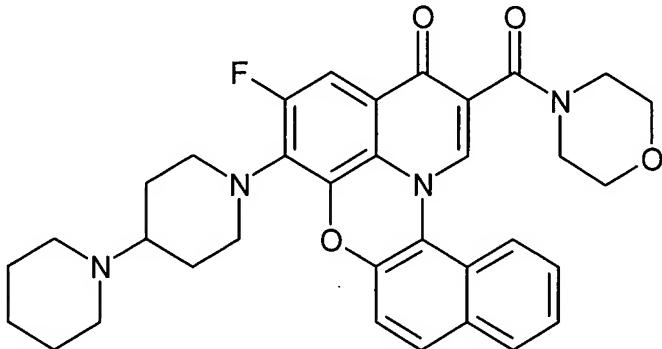
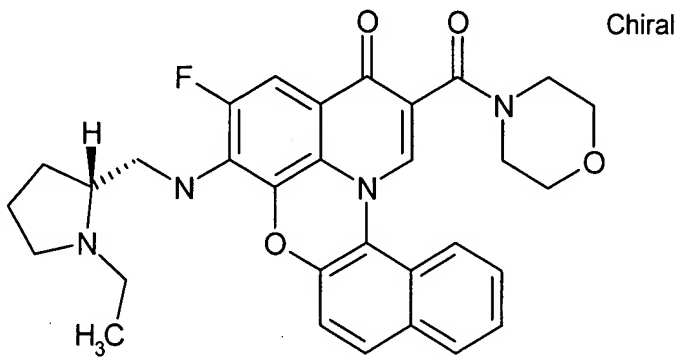
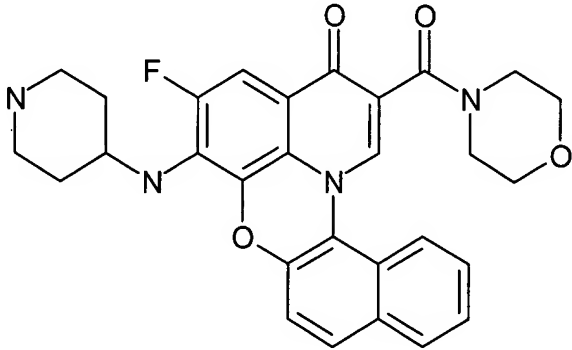
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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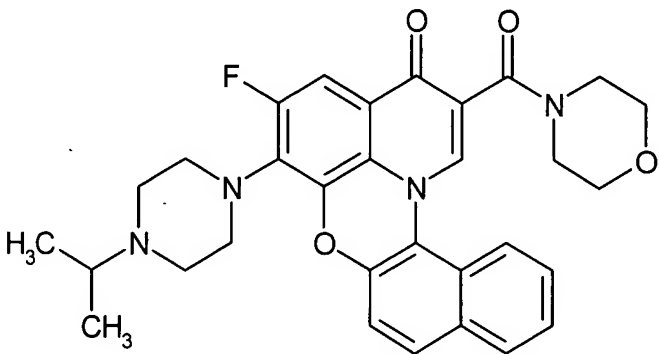
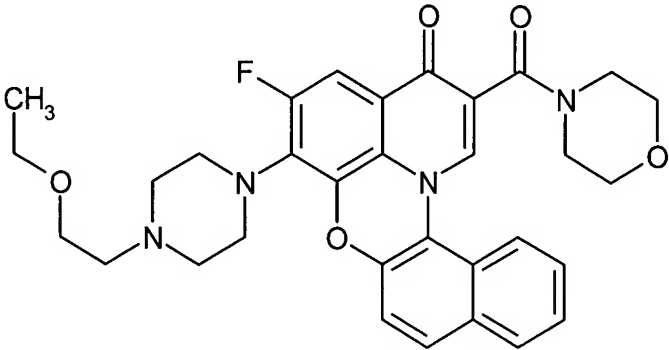
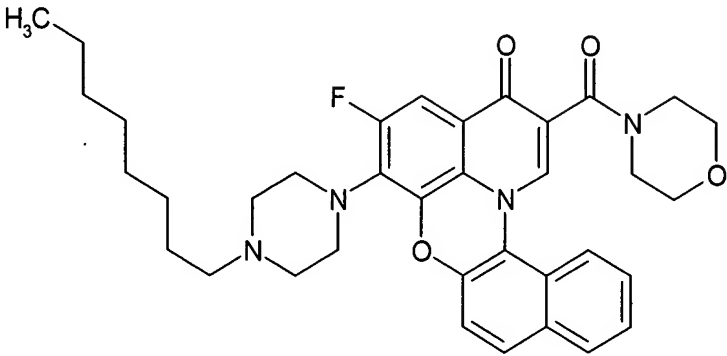
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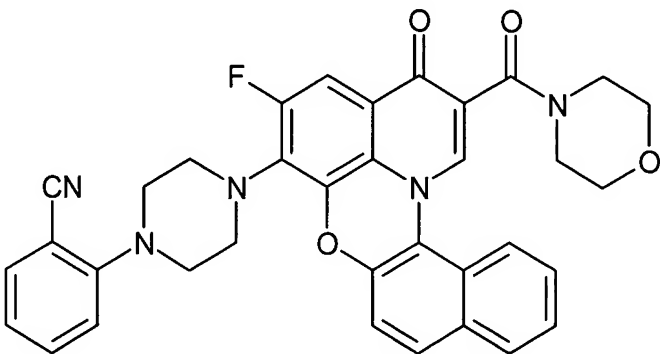
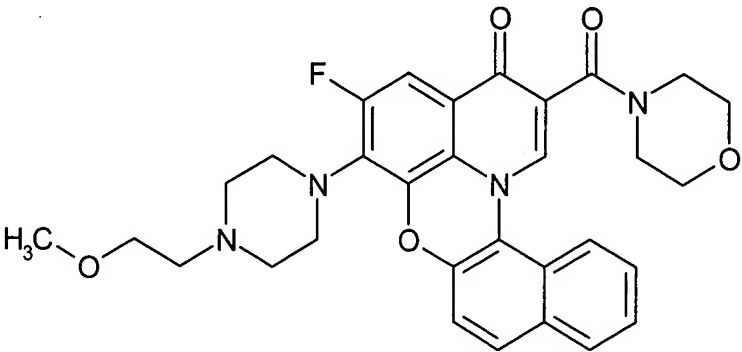
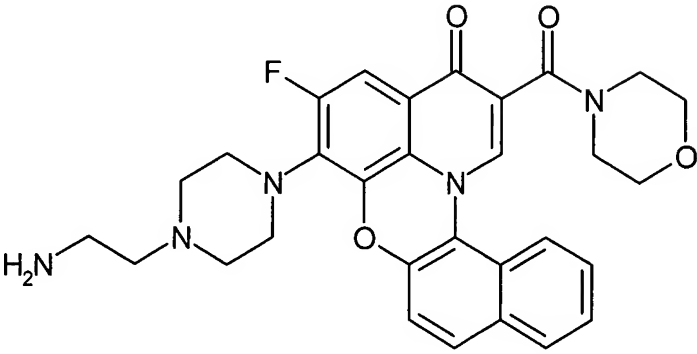
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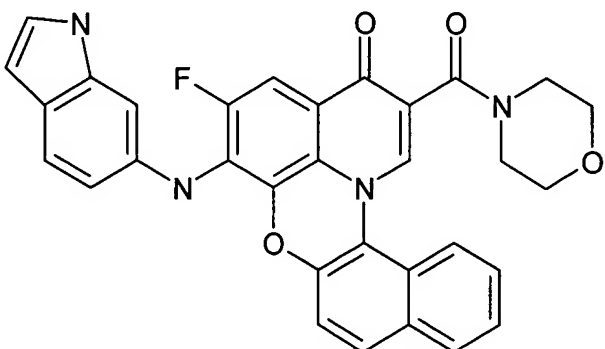
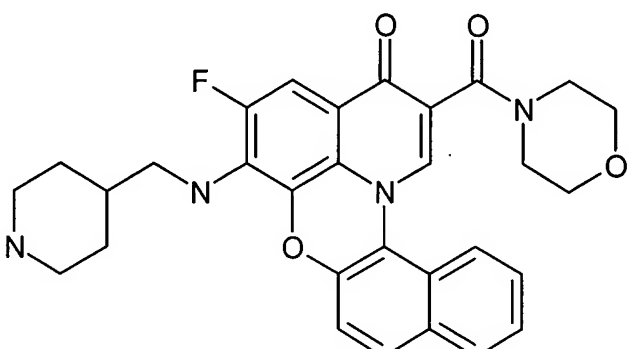
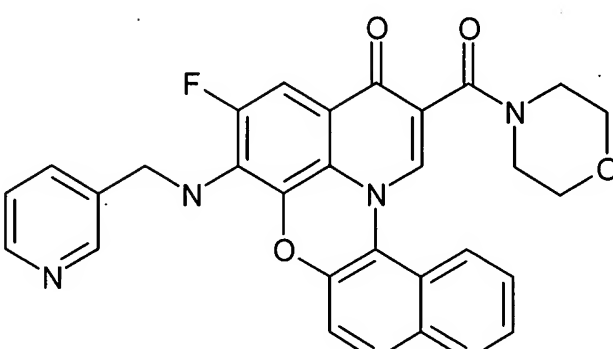


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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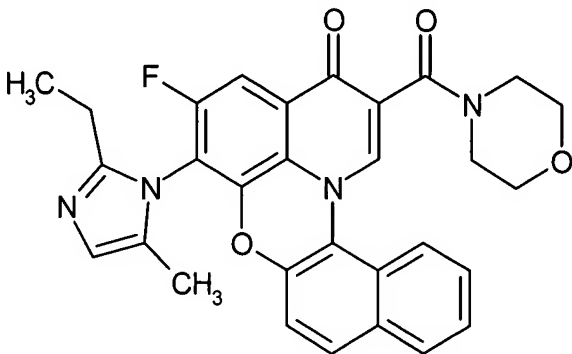
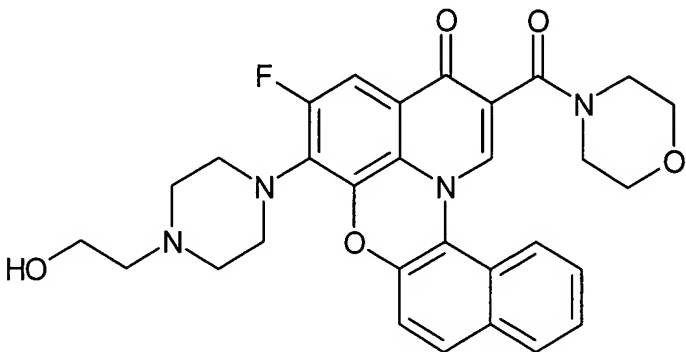
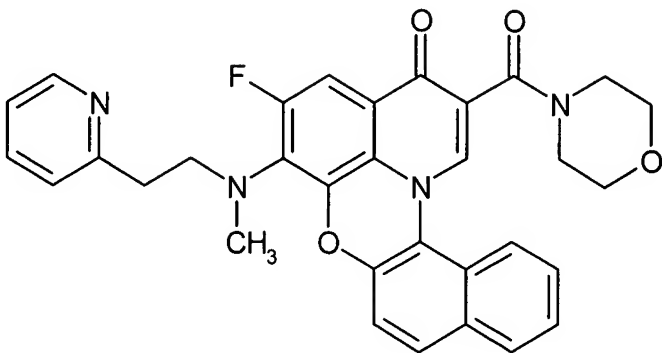
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959			
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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962			
963			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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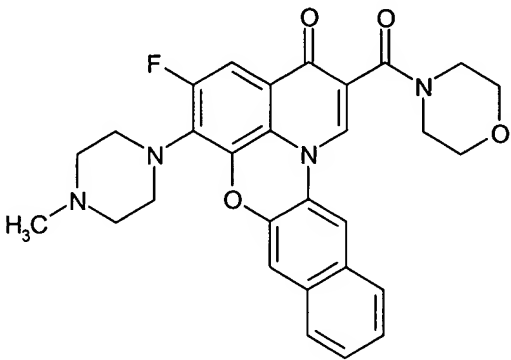
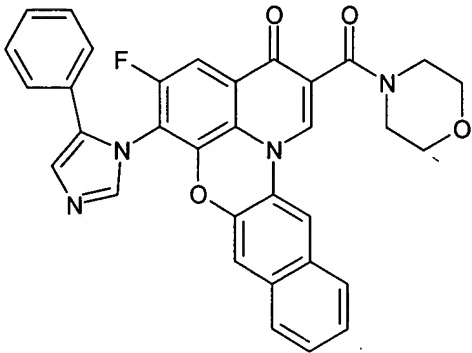
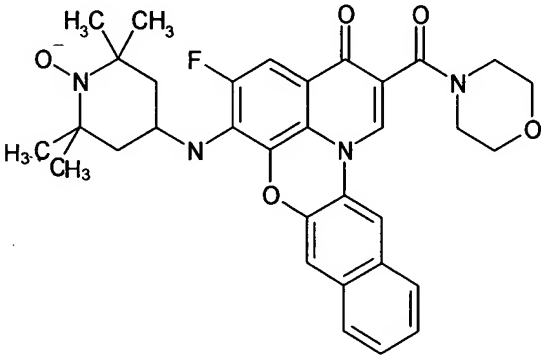
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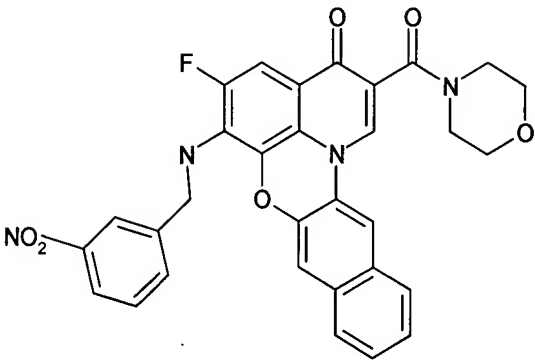
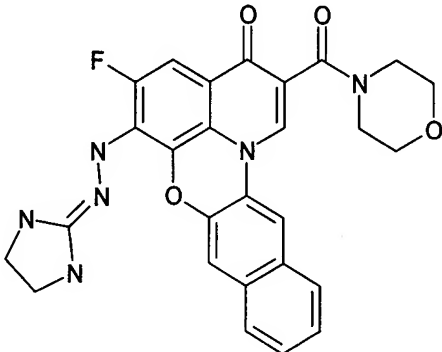
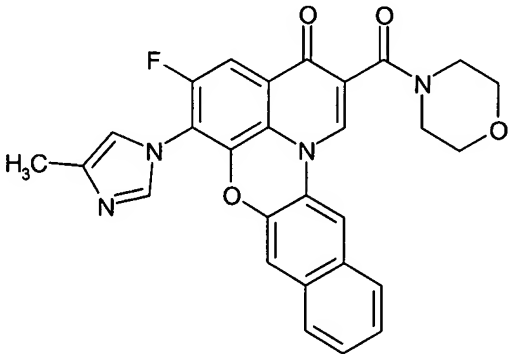
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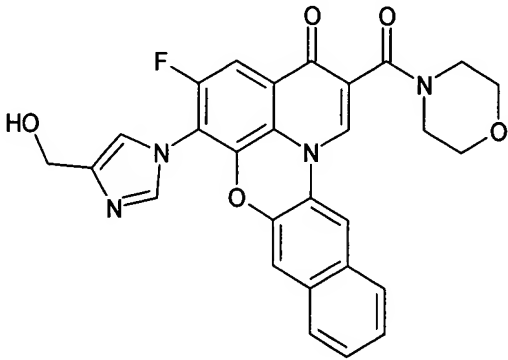
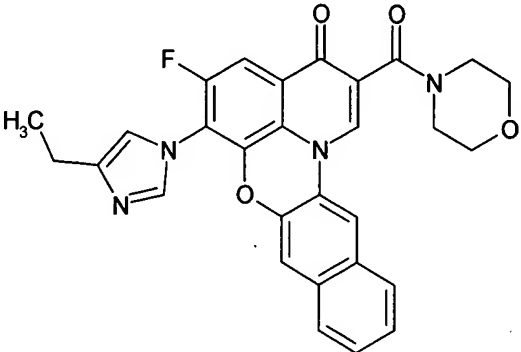
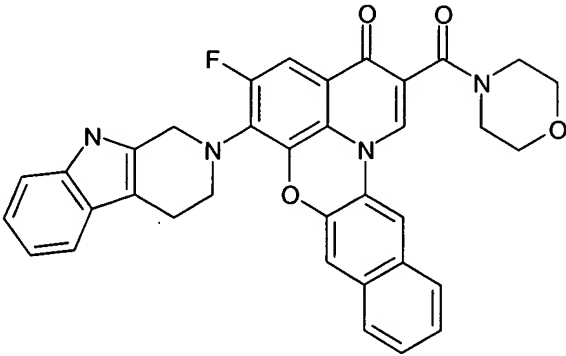
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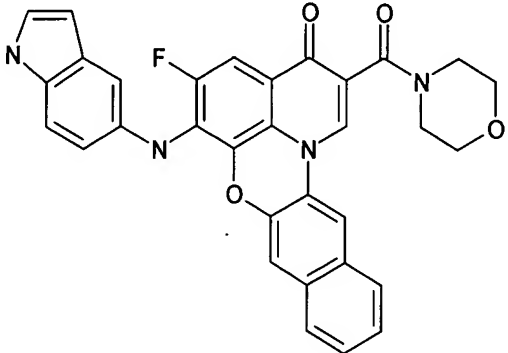
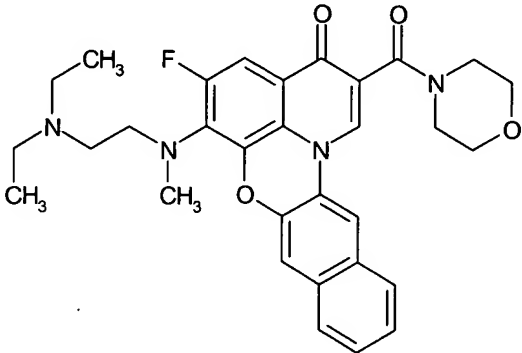
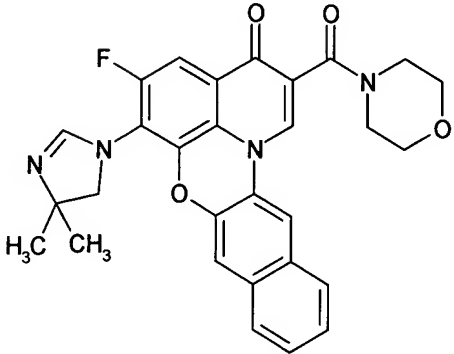


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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981			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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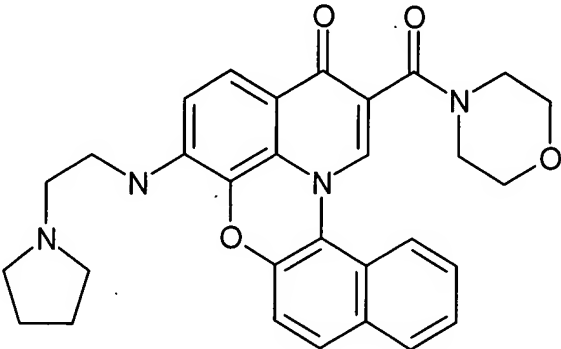
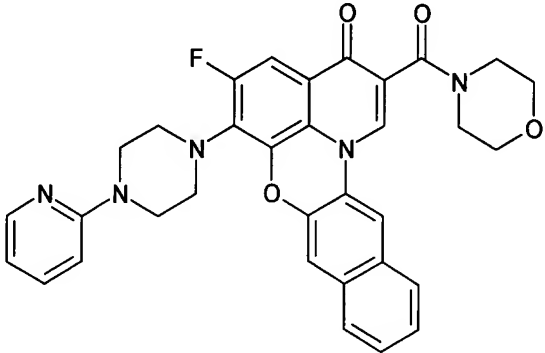
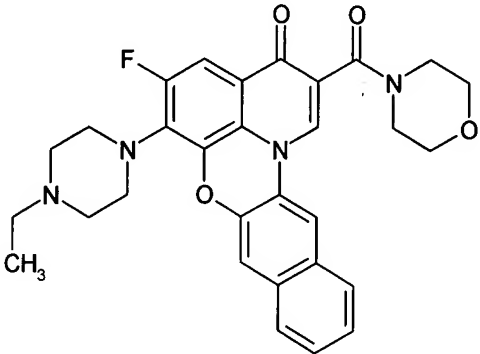
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
988			
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990			

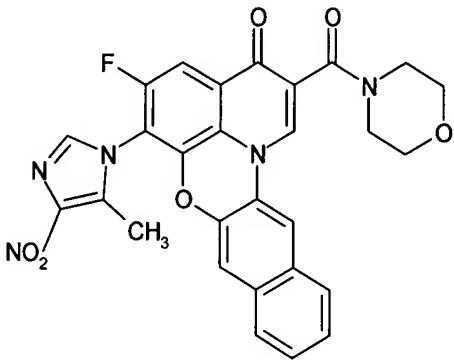
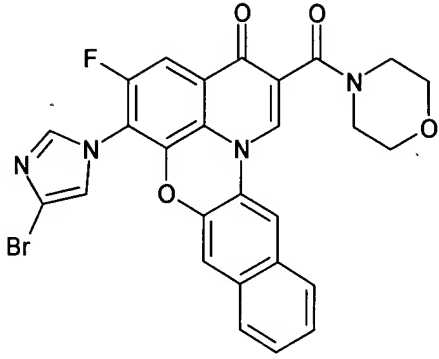
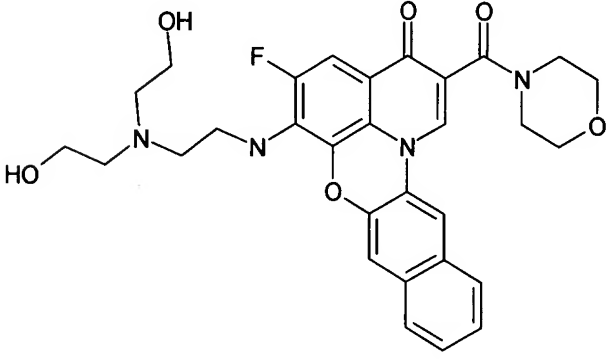
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
991			
992			
993			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
994			
995			
996			

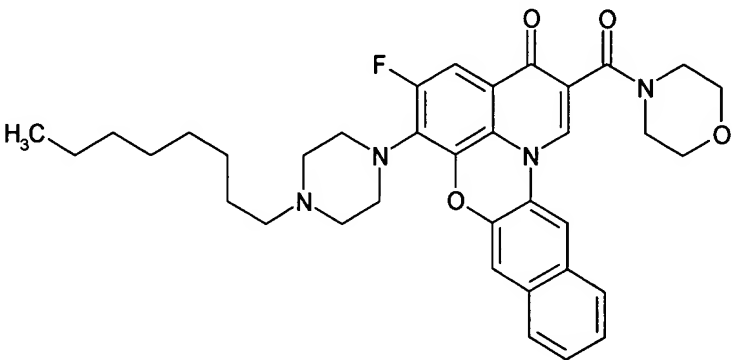
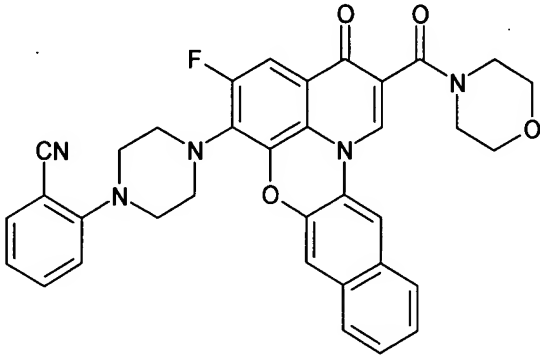
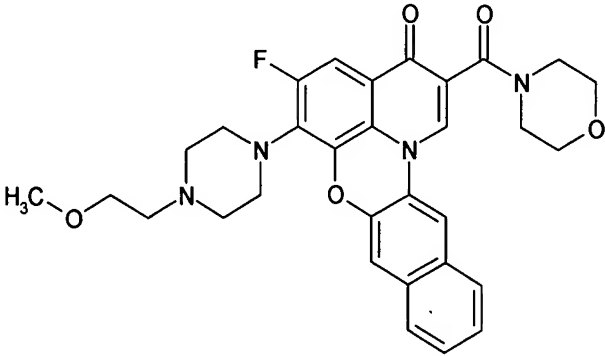
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
997			
998			
999			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1000			
1001			
1002			

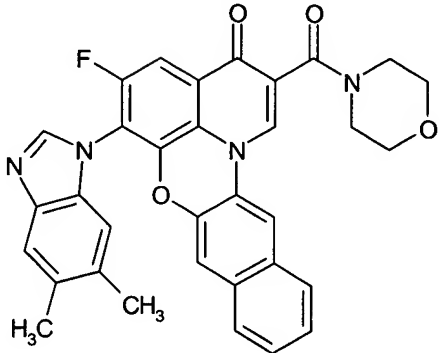
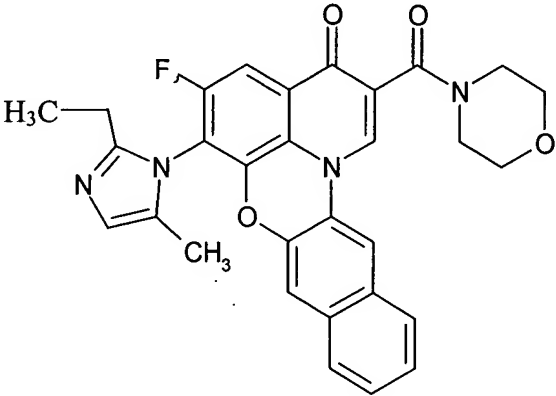
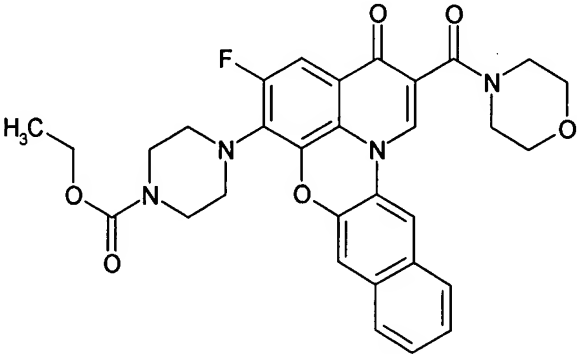


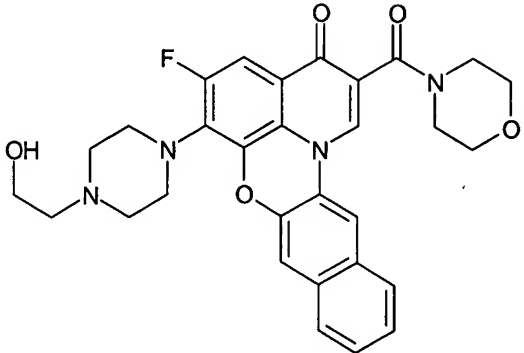
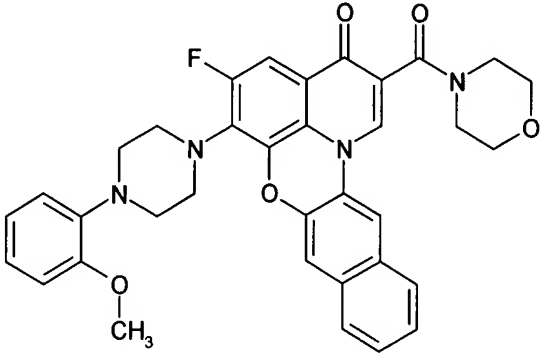
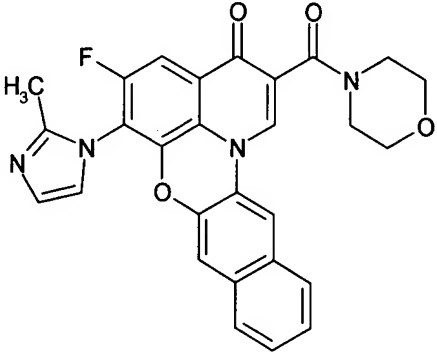
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1003			
1004			
1005			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1007			
1008			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1009			
1010			
1011			



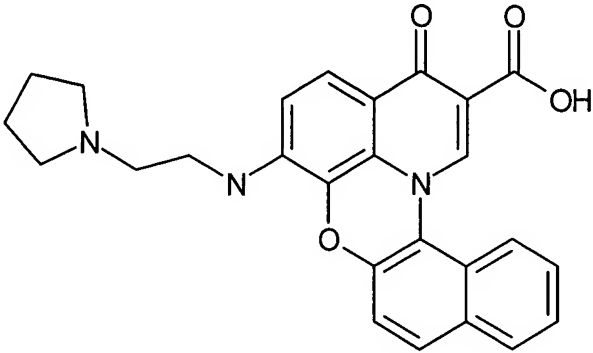
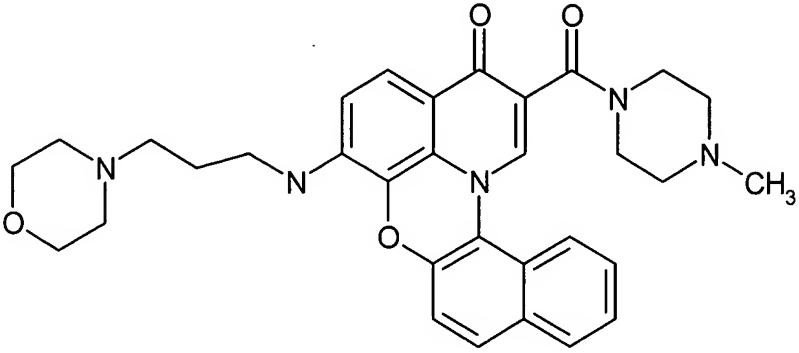
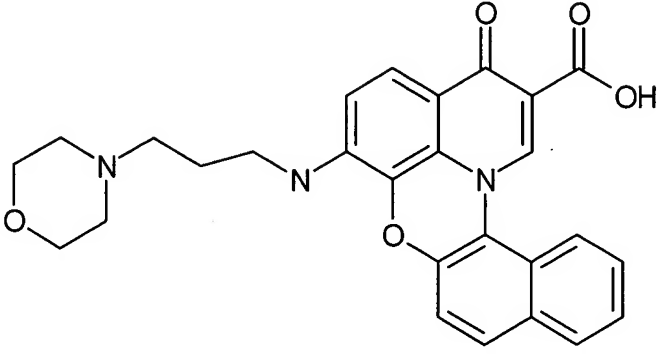
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1016			
1017			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1023			

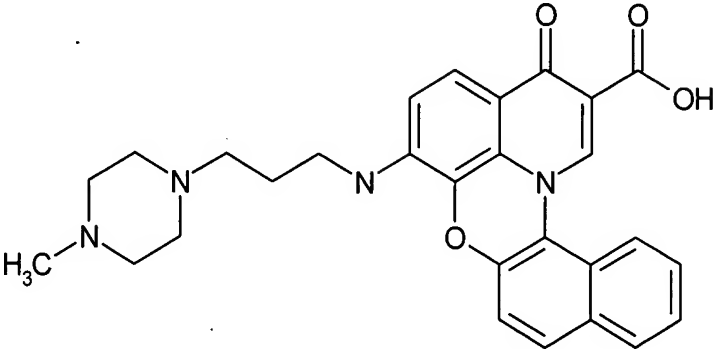
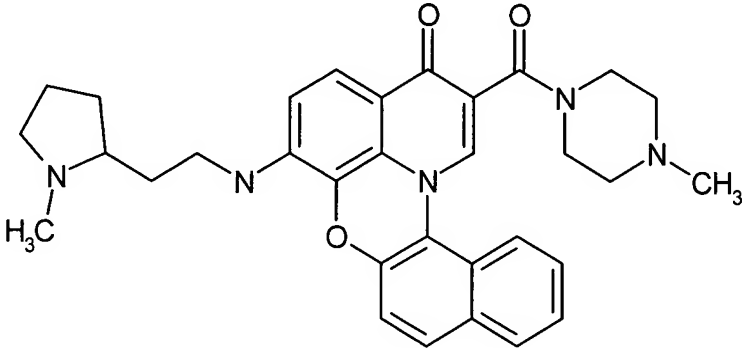
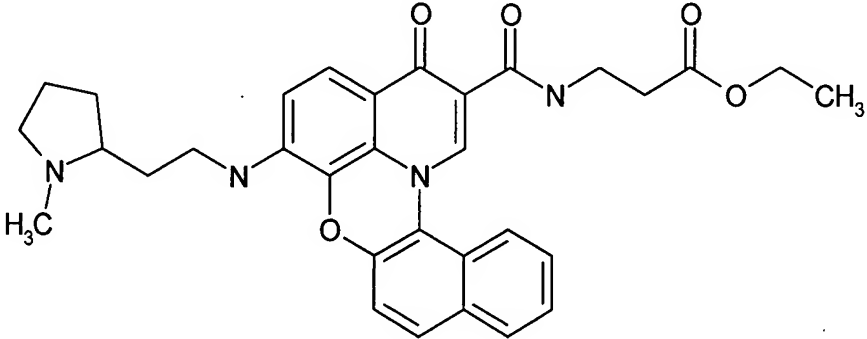
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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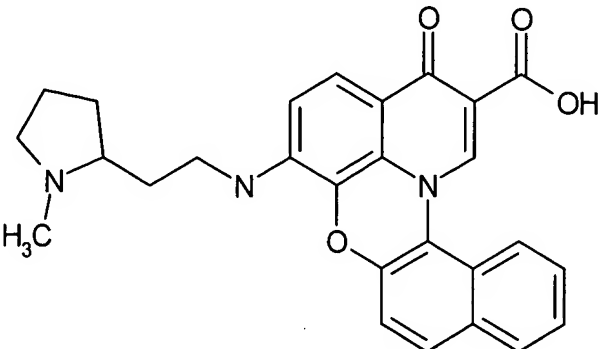
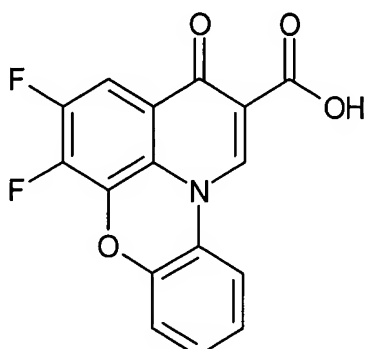
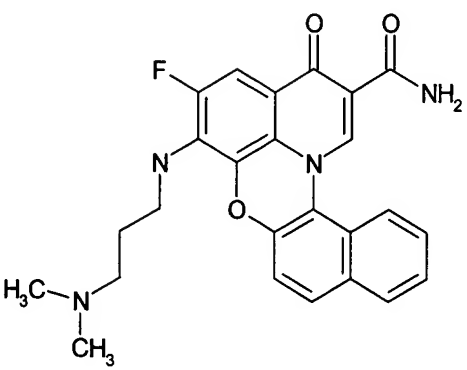


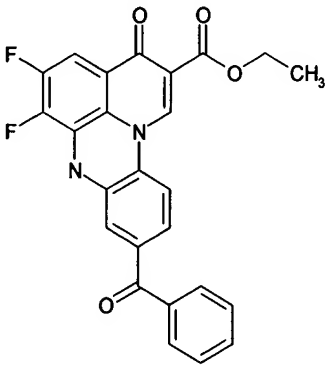
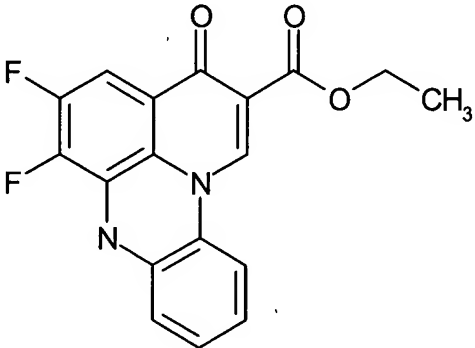
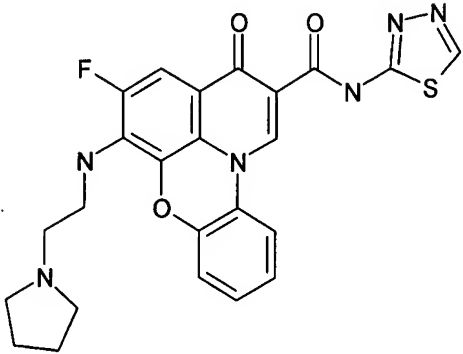
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1027			
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1029			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1032			

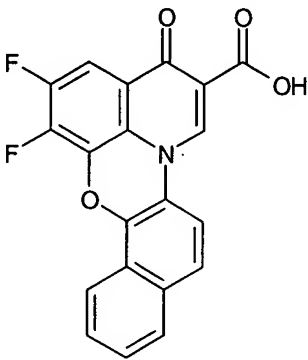
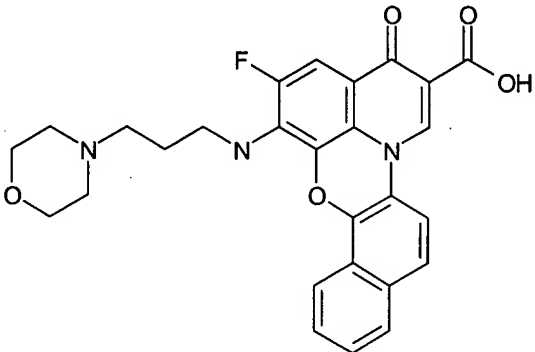
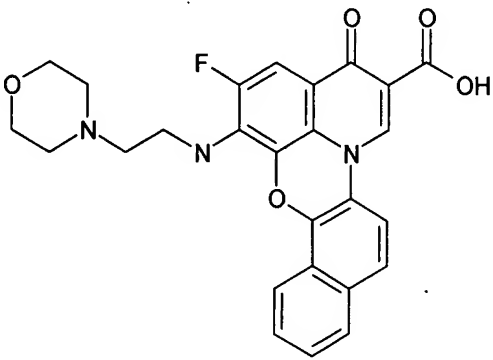
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1037			
1038			

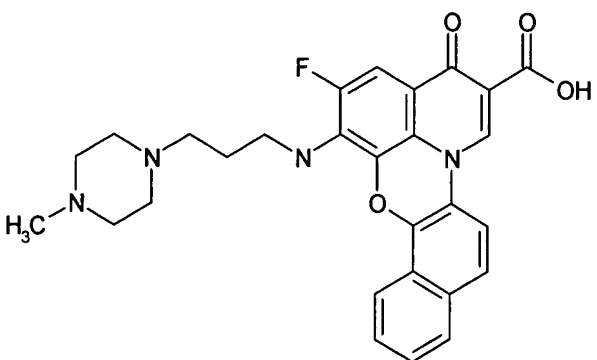
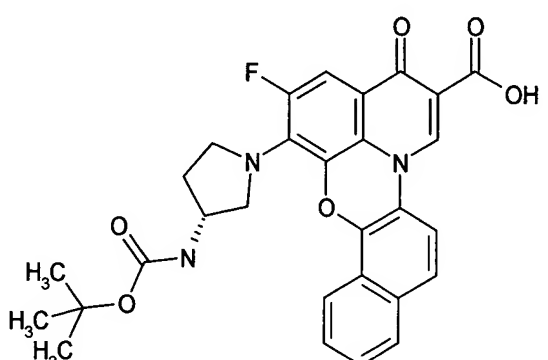
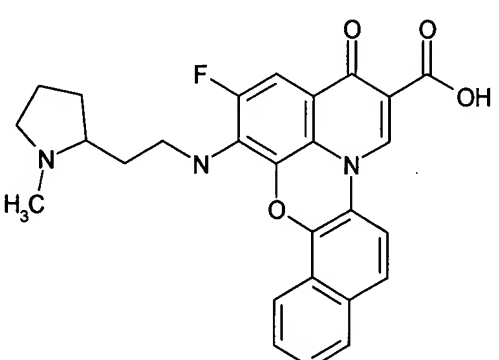
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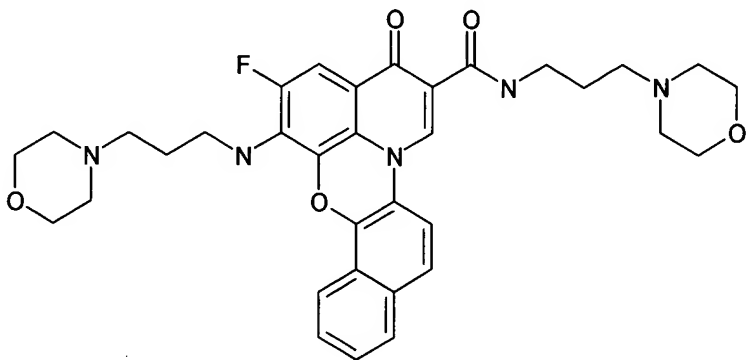
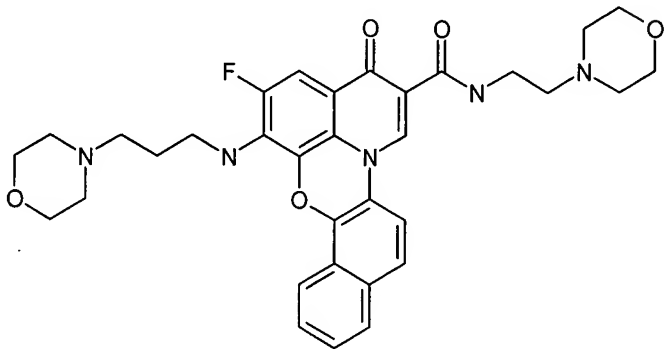
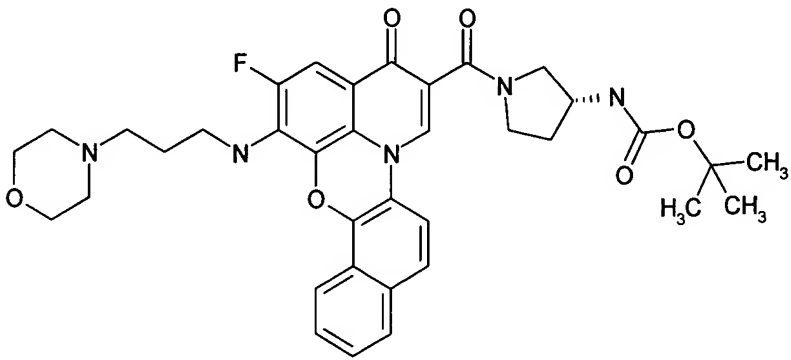
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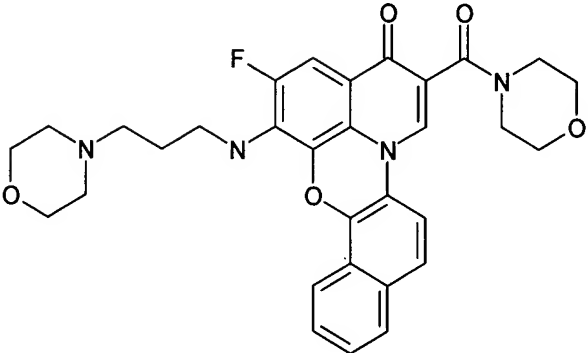
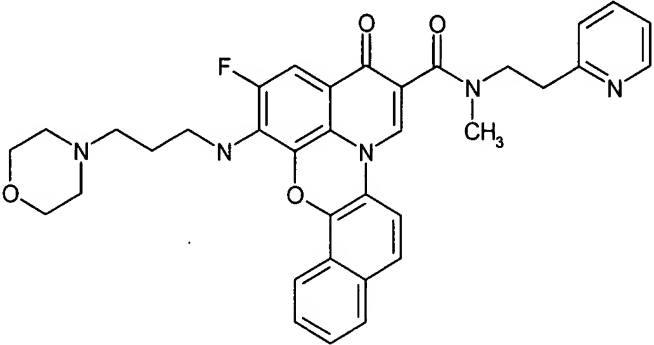
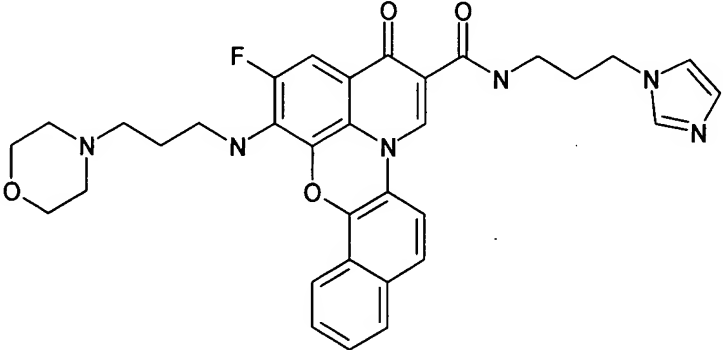
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1047			

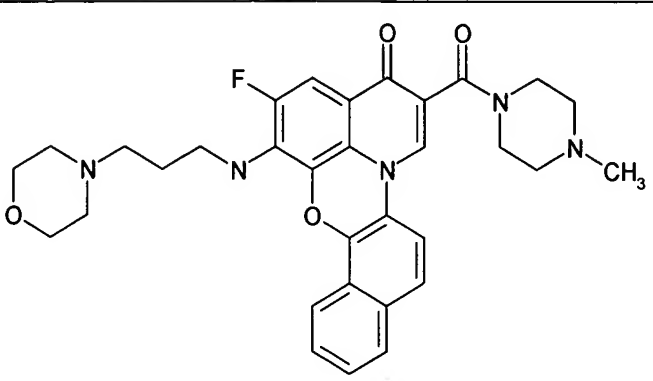
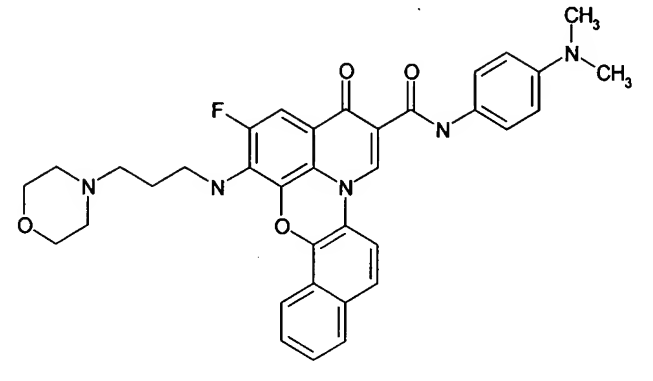
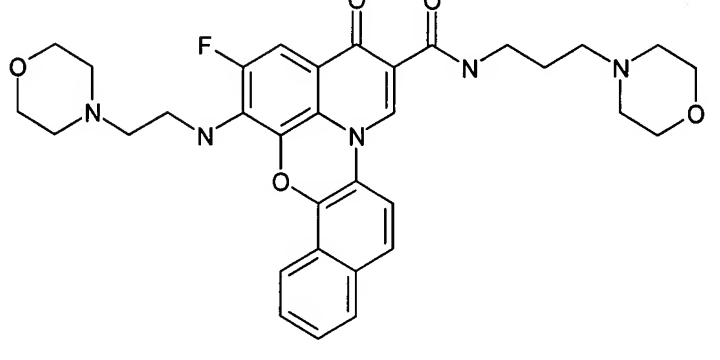
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1050			

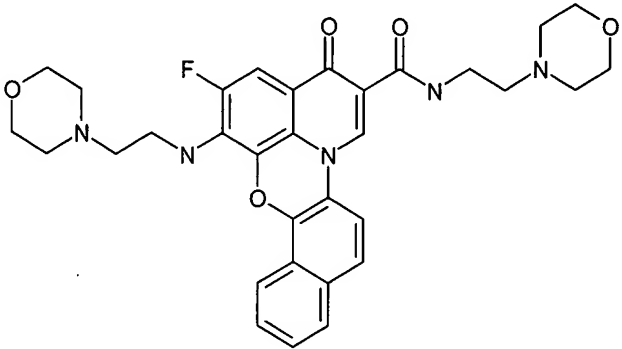
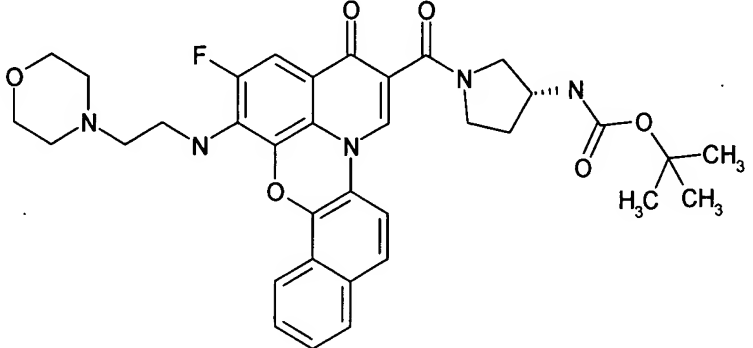
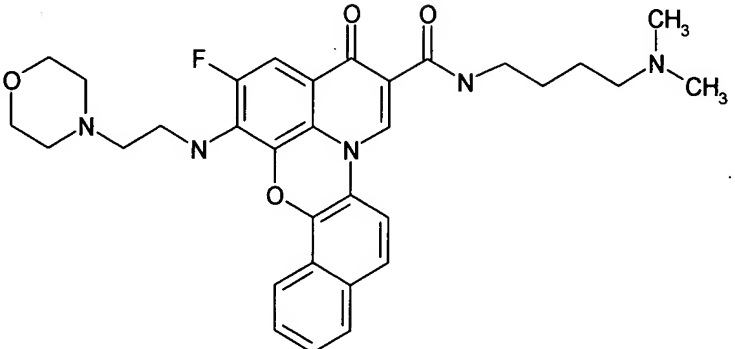


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1053			

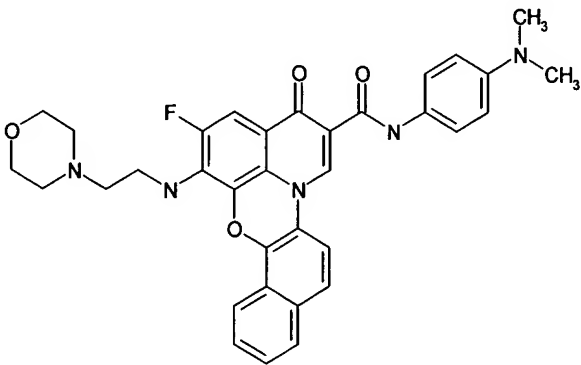
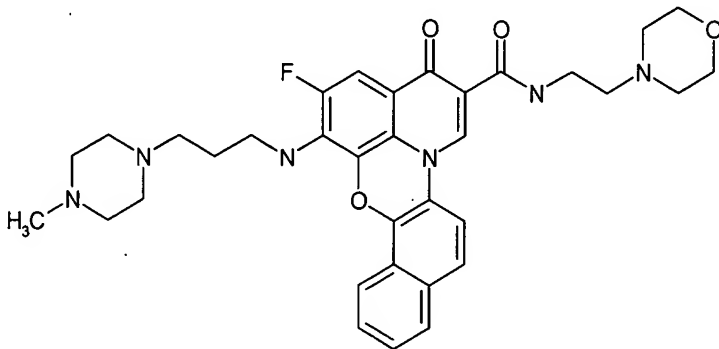
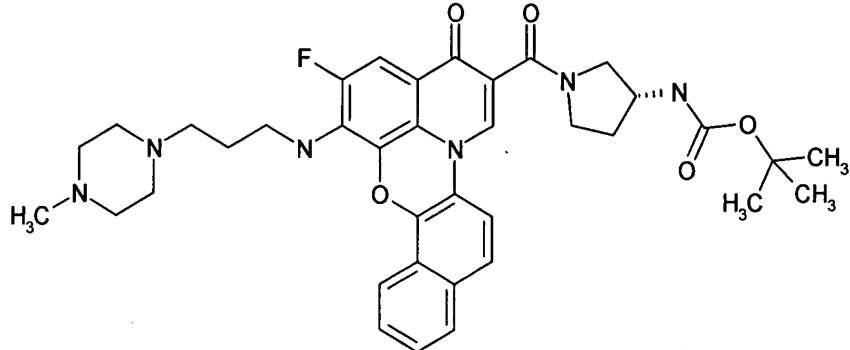
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1054			
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1056			

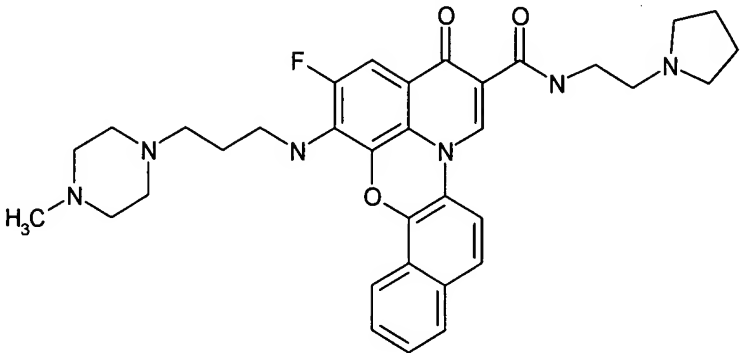
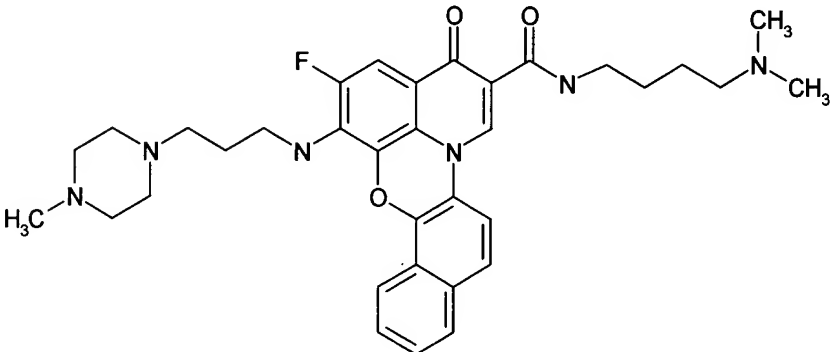
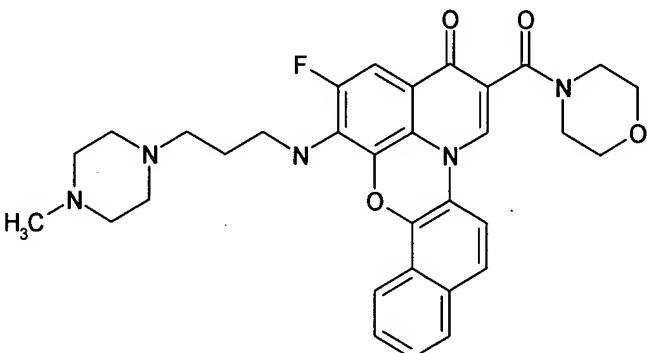
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1059			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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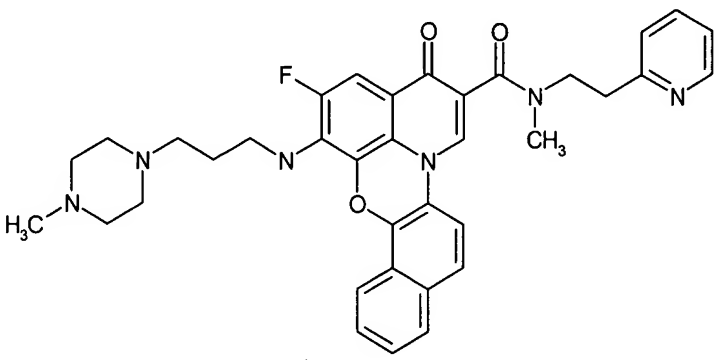
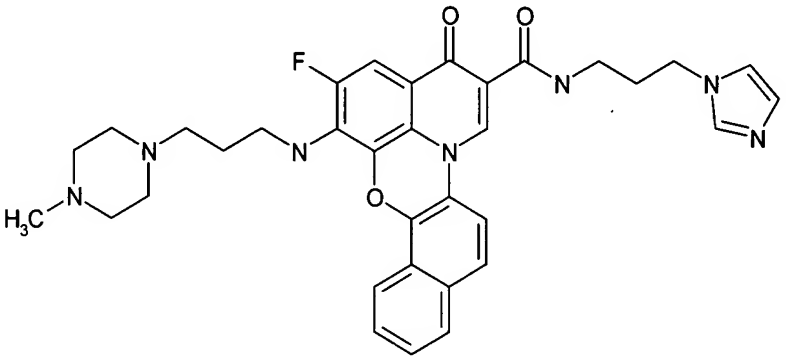
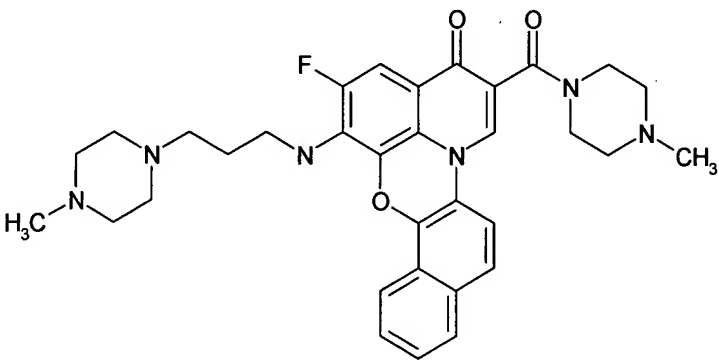
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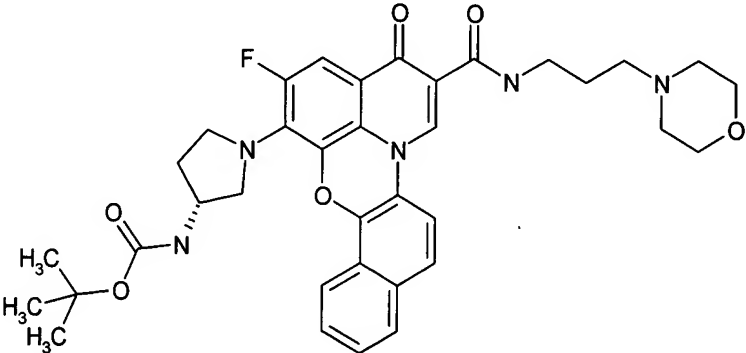
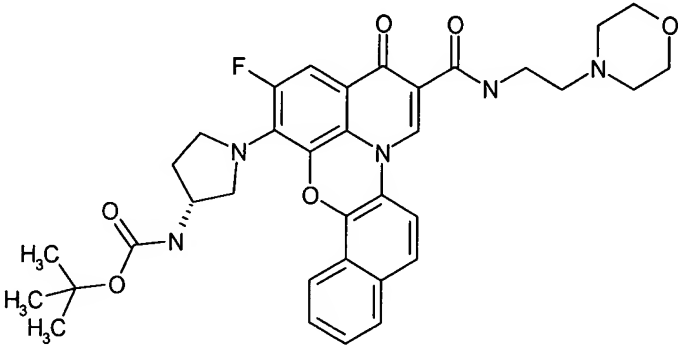
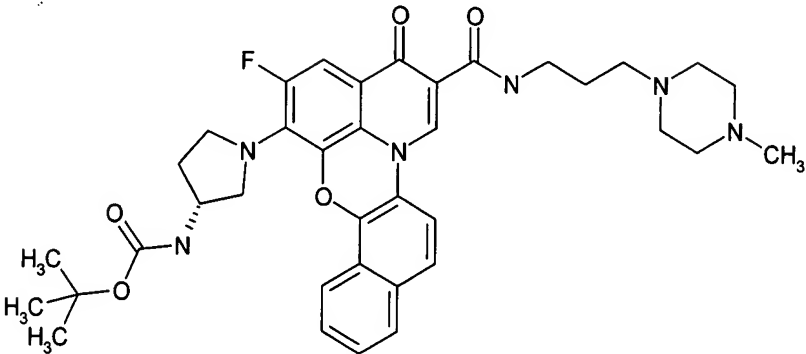
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1067			
1068			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1071			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1073			
1074			



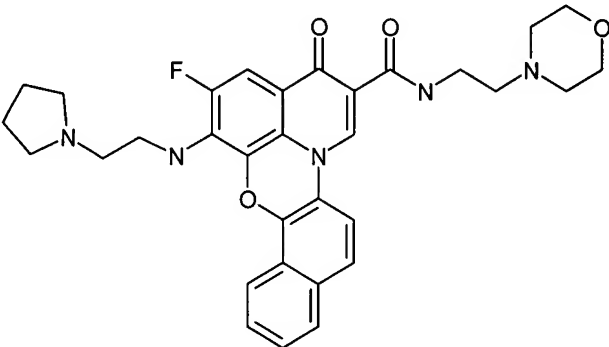
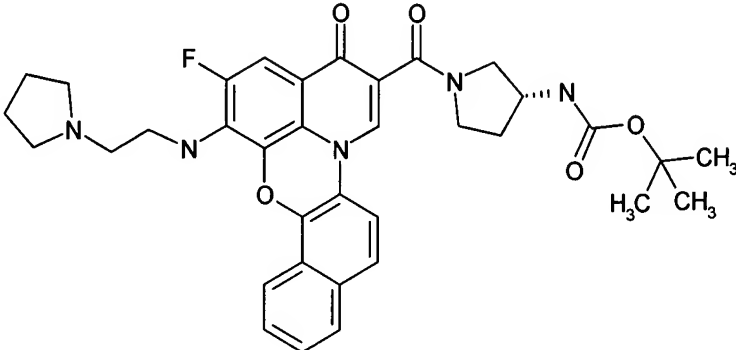
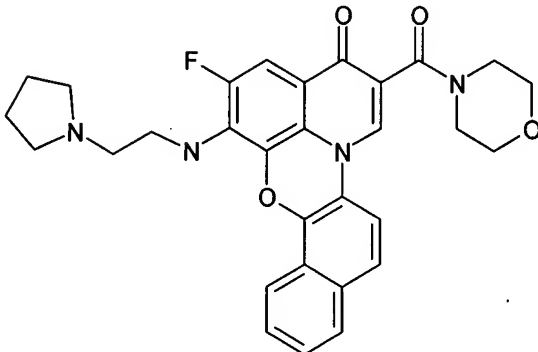
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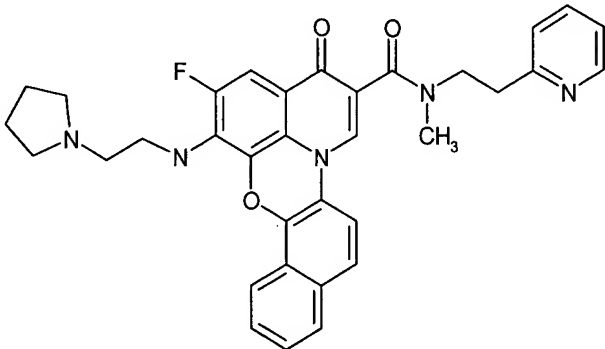
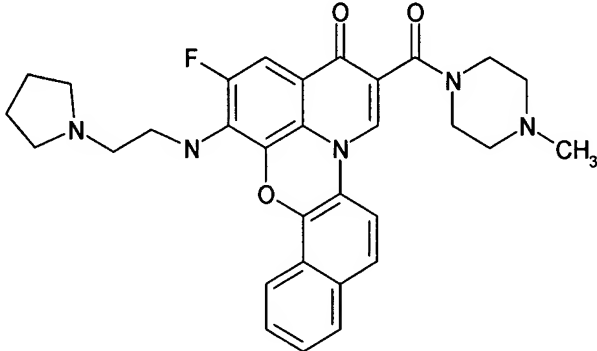
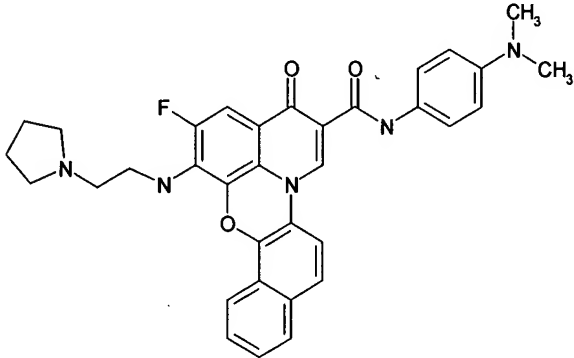
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1080			

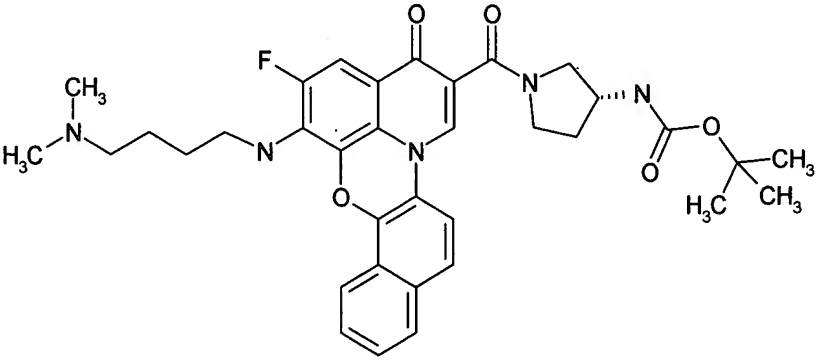
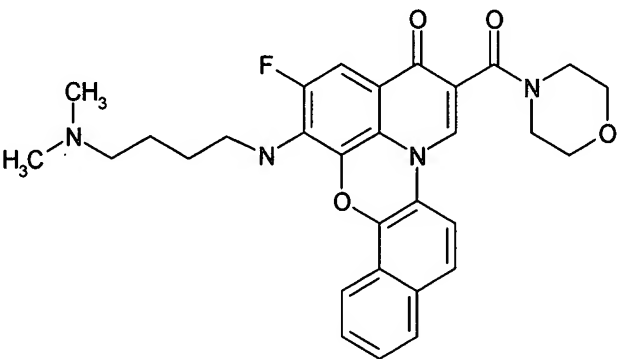
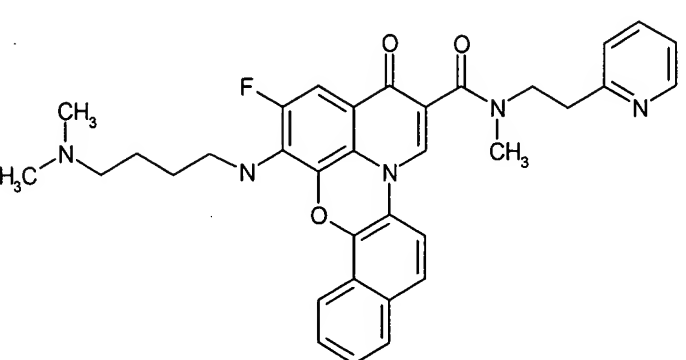
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1083			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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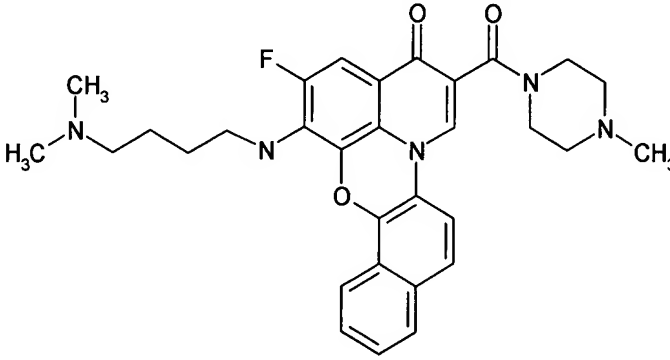
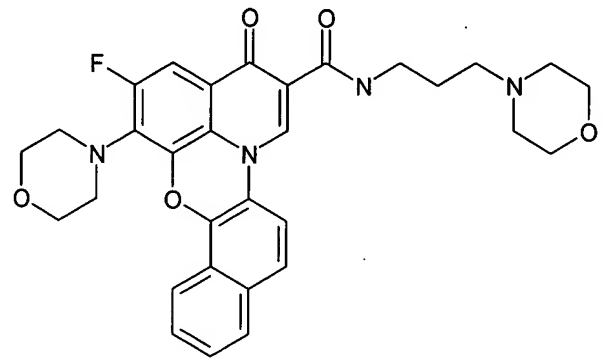
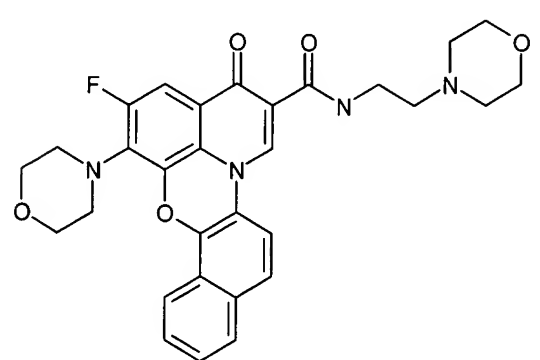
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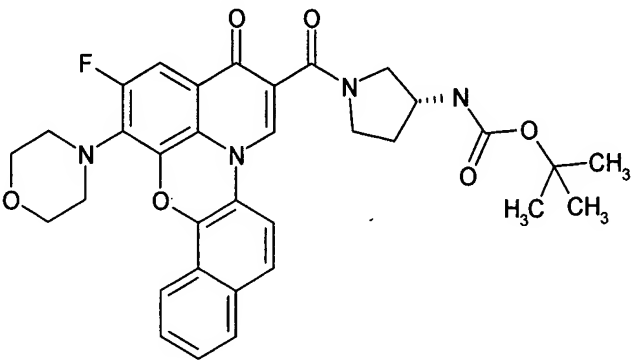
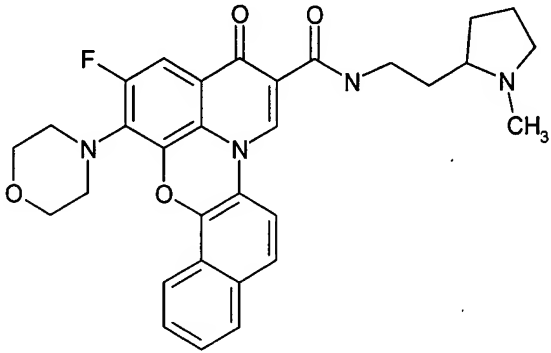
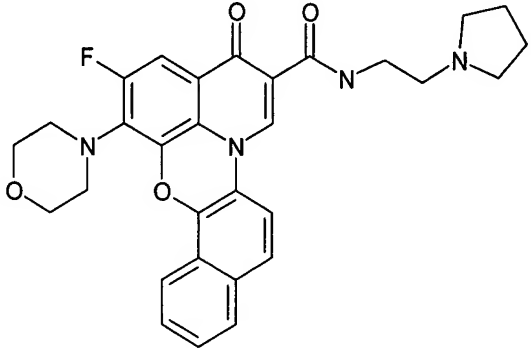
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1092			

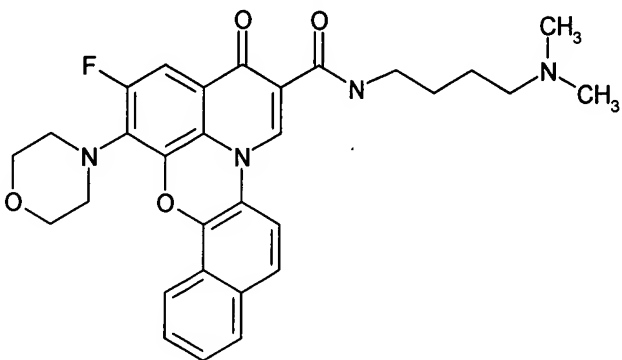
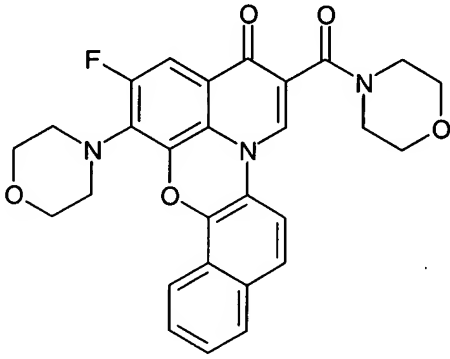
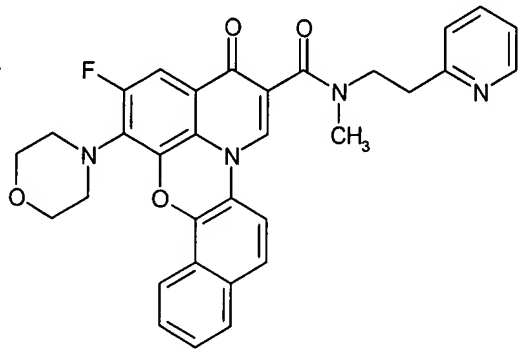
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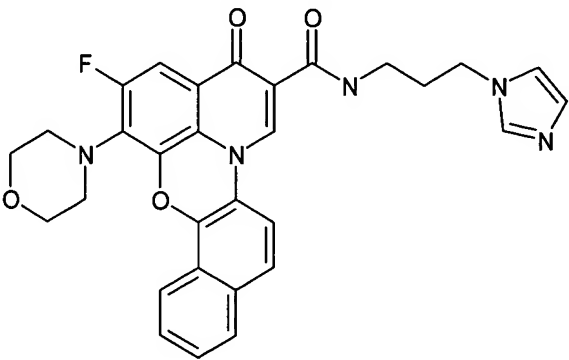
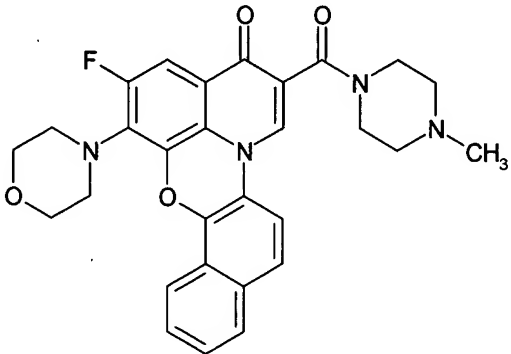
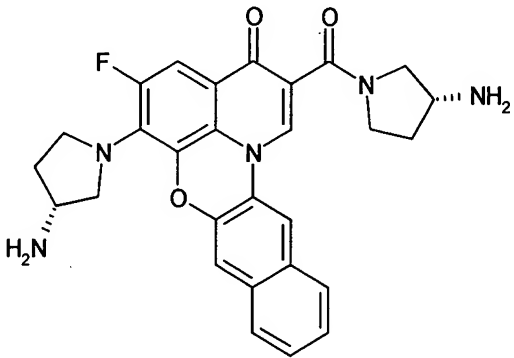
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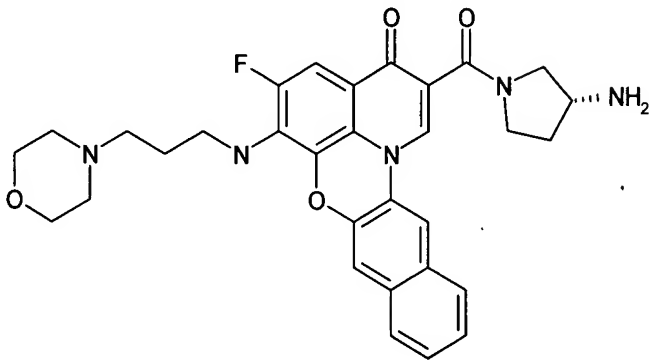
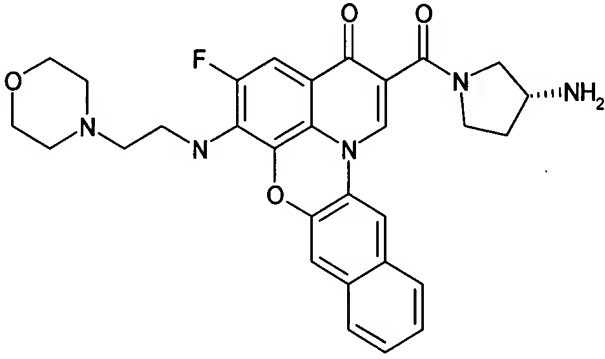
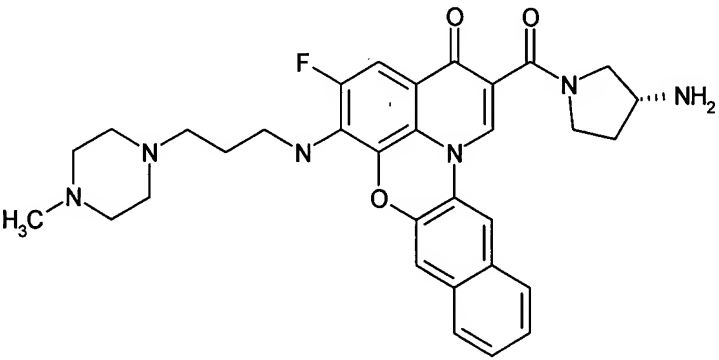


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1099			
1100			
1101			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1102			
1103			
1104			

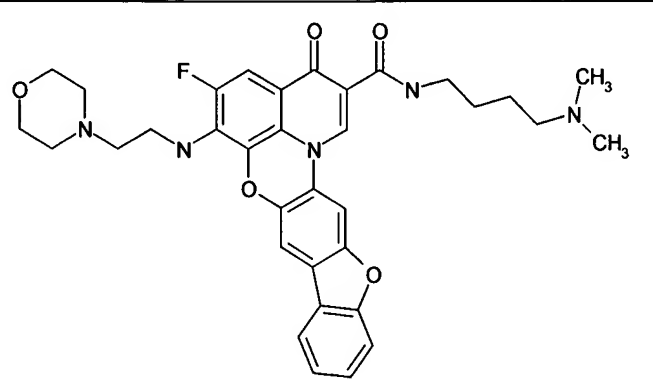
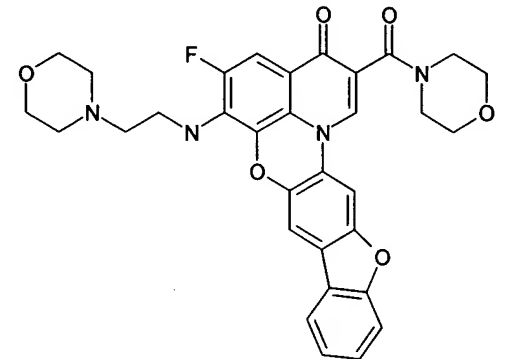
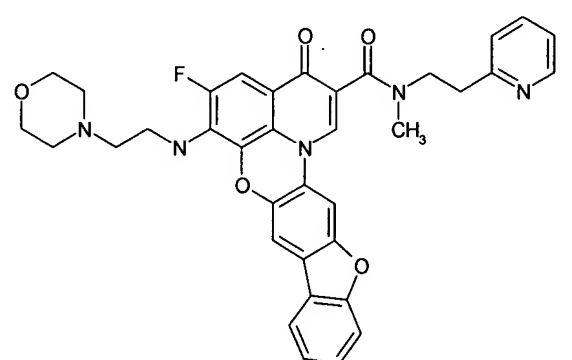
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1107			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1108			
1109			
1110			

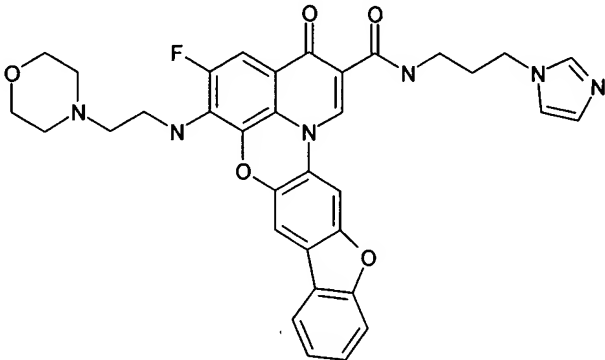
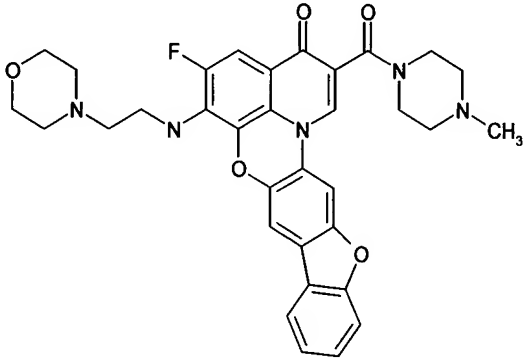
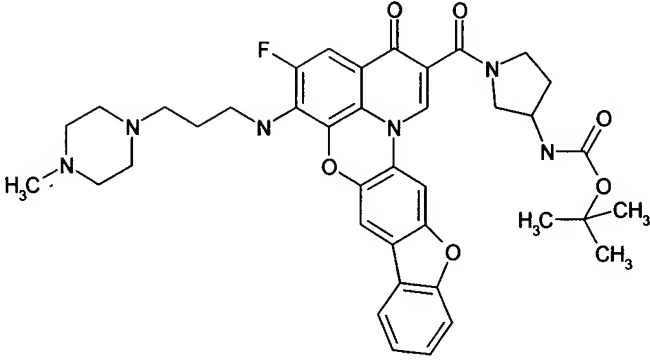
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1111			
1112			
1113			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1114			
1115			
1116			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1119			

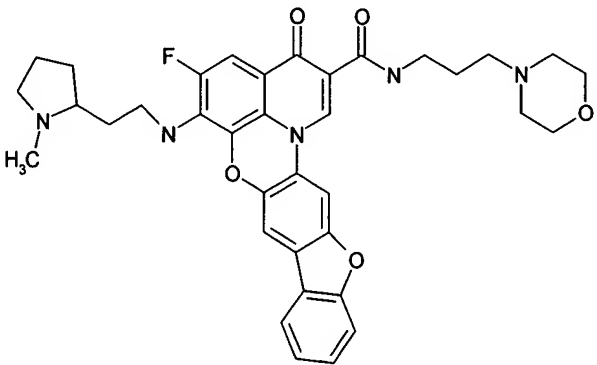
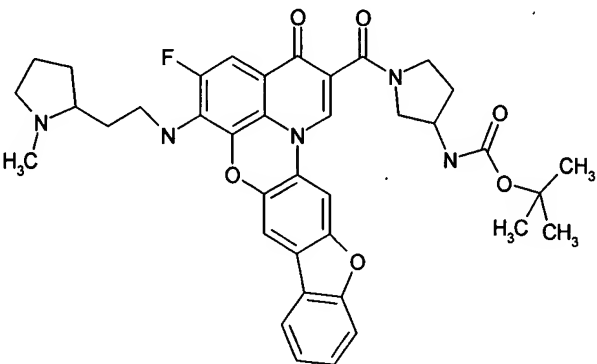
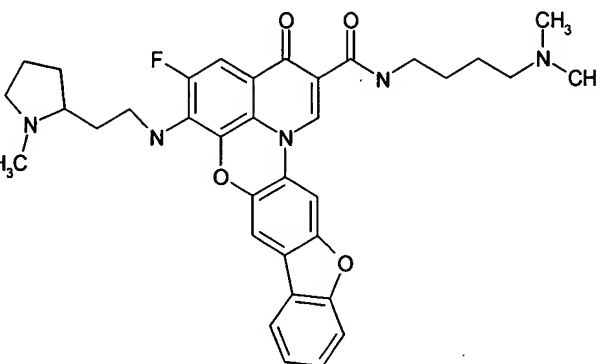
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1121			
1122			

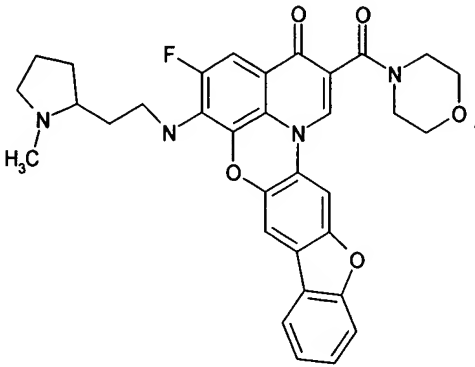
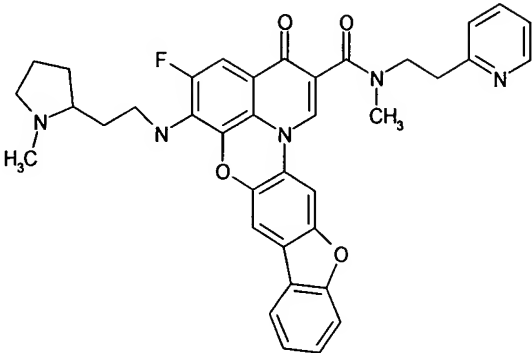
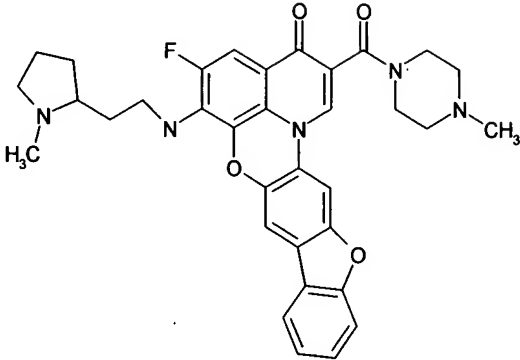


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1124			
1125			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1127			
1128			

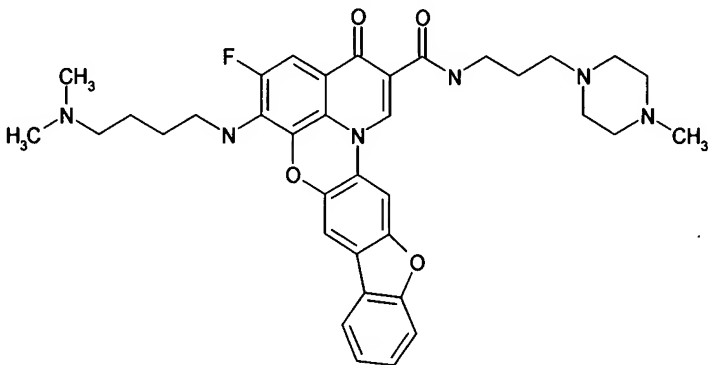
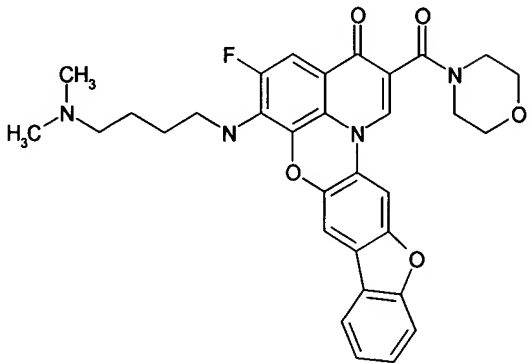
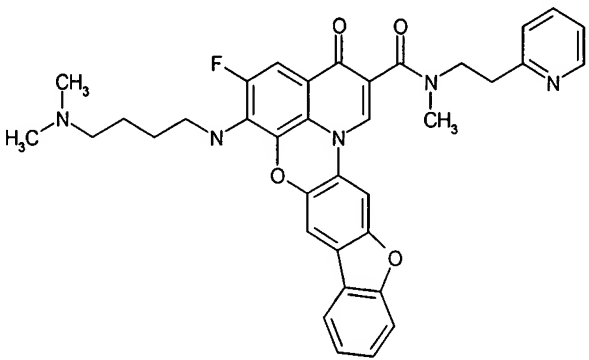
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1131			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1132			
1133			
1134			

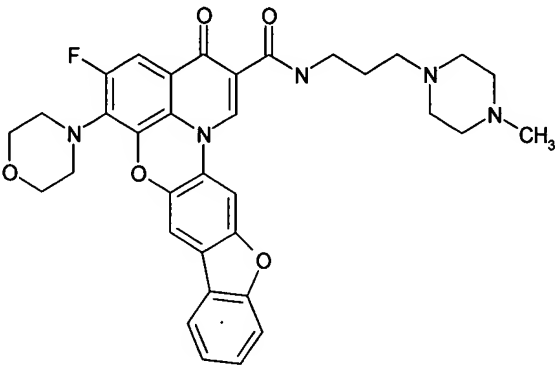
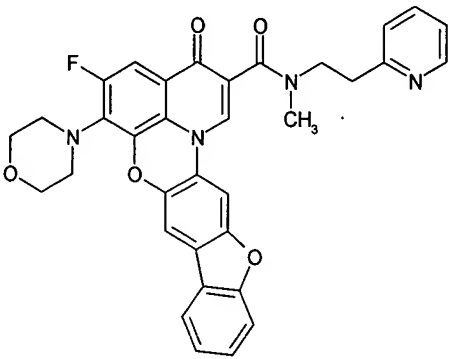
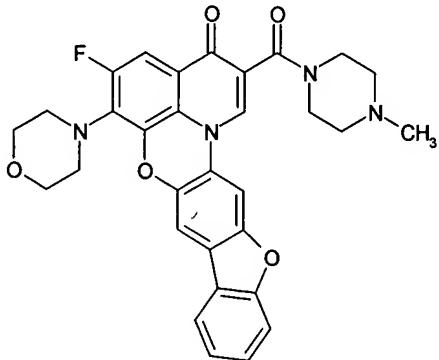
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1137			

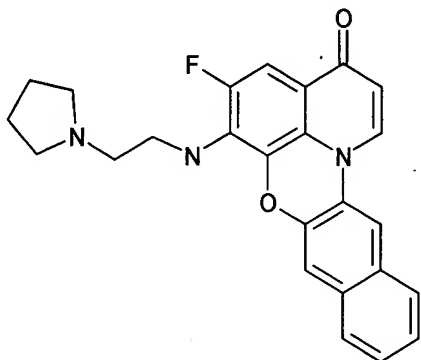
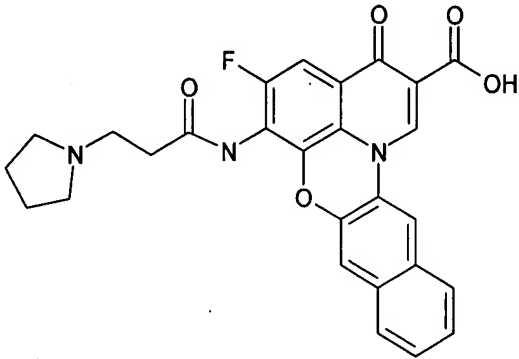
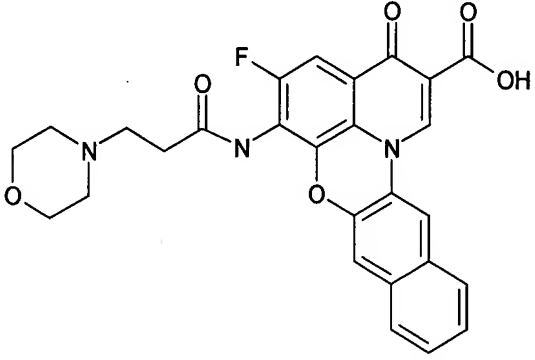
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1140			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1142			
1143			

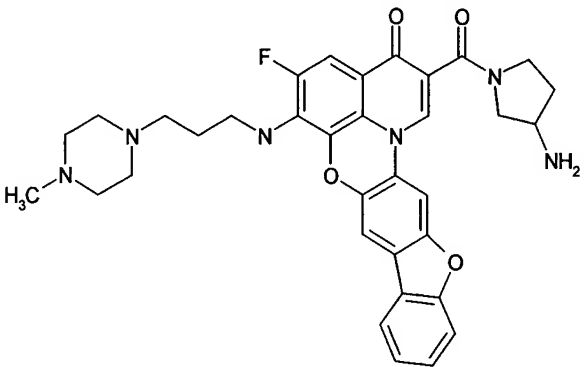
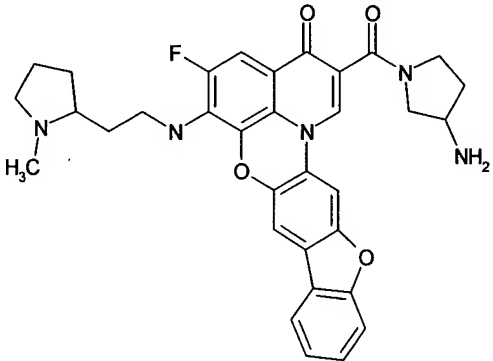
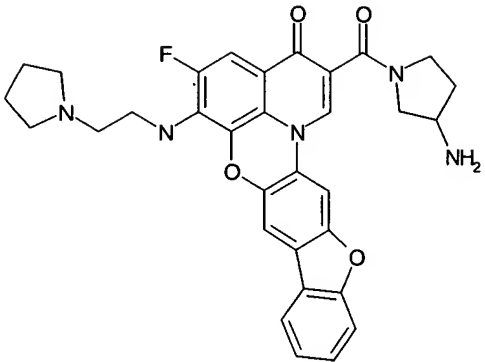
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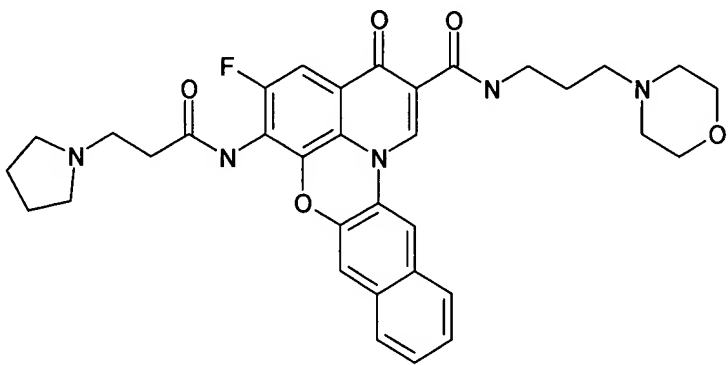
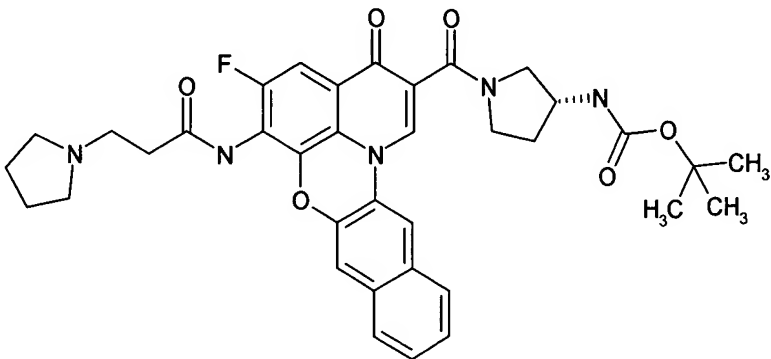
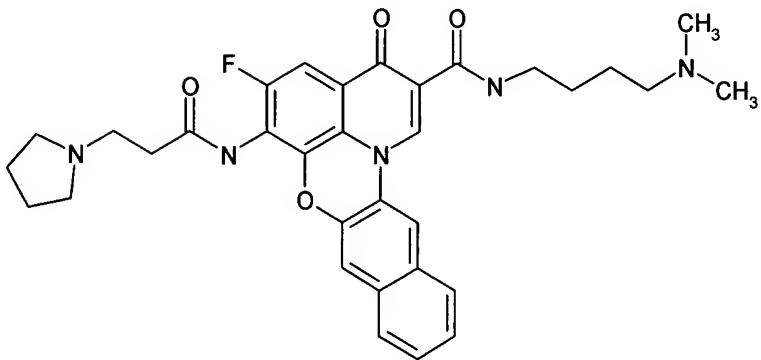


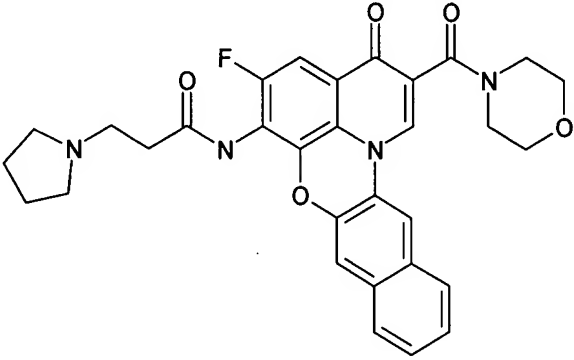
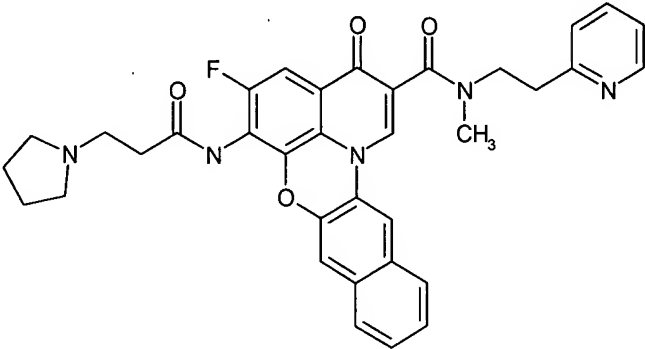
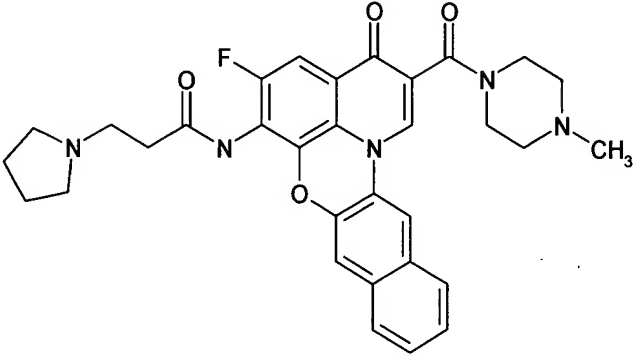
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1149			

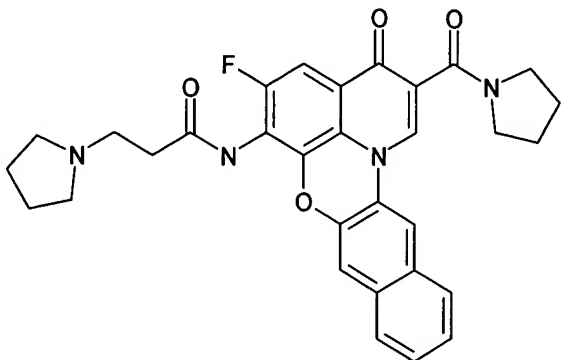
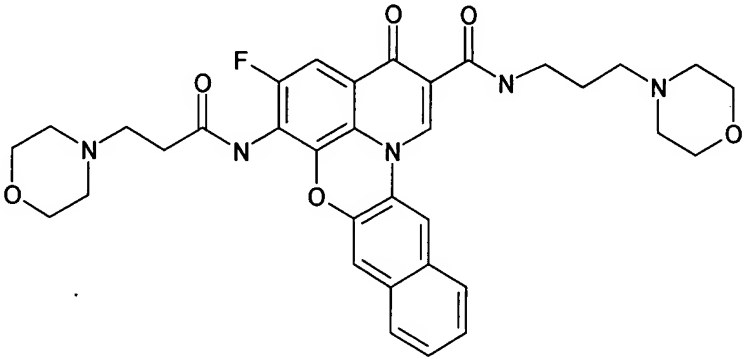
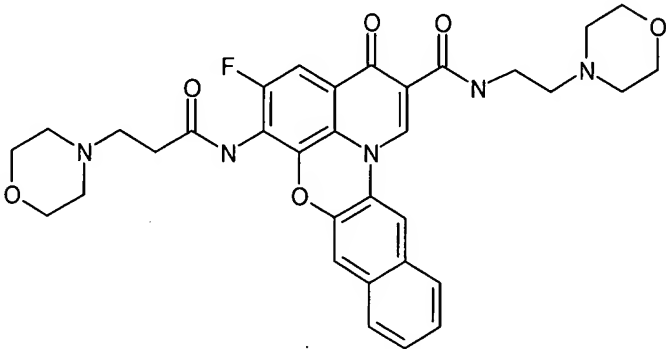
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1152			

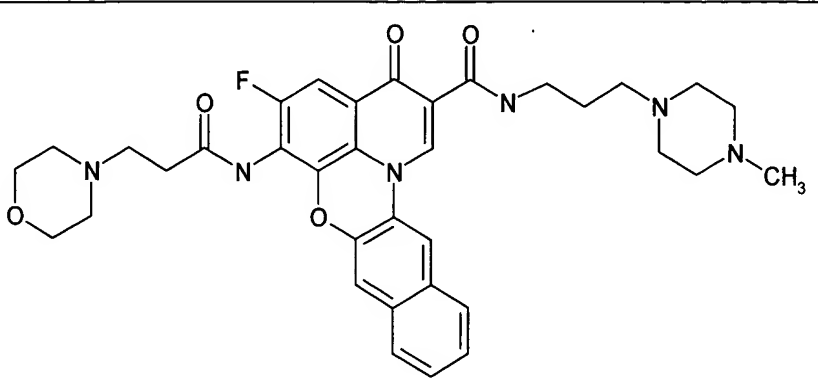
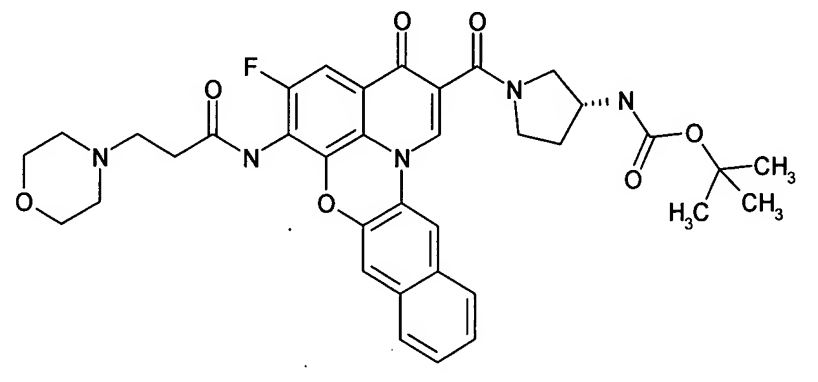
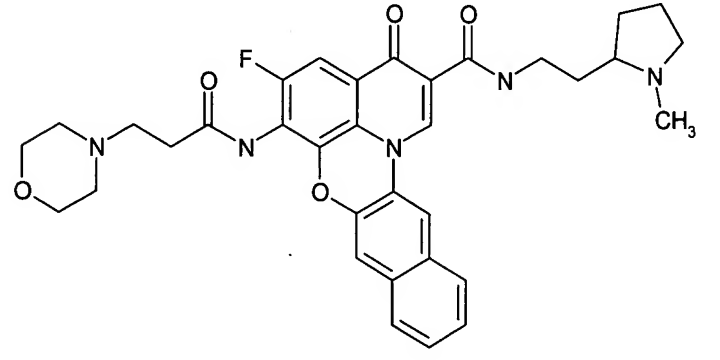
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1155			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1158			

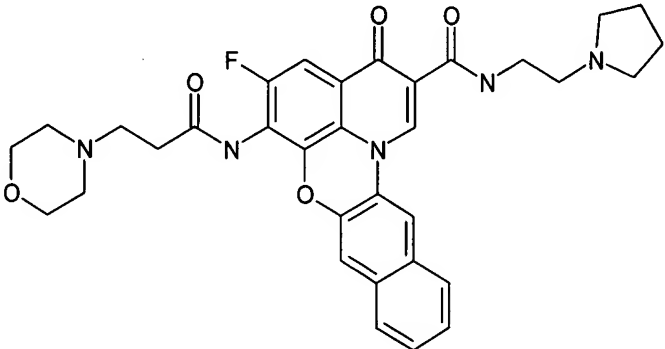
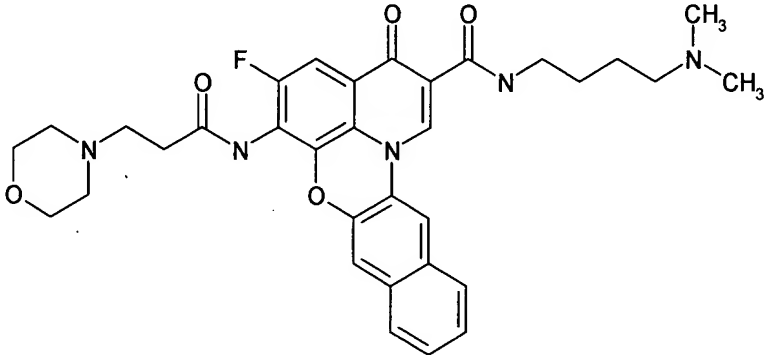
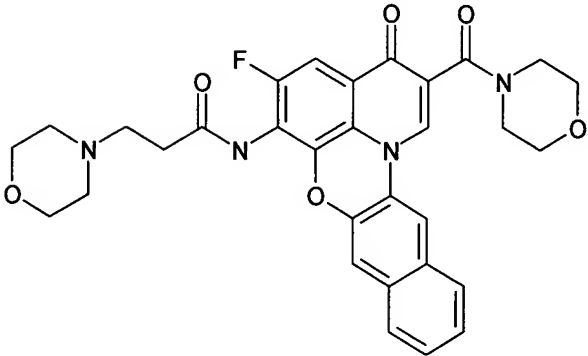
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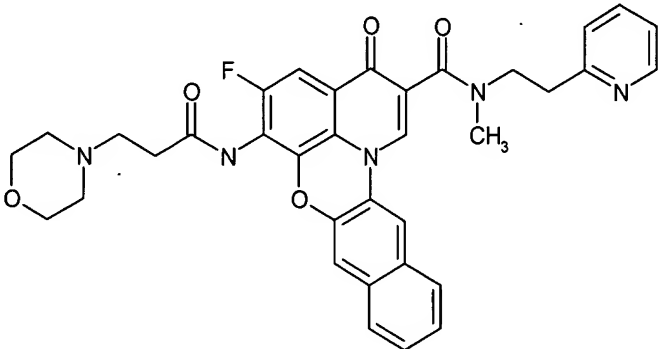
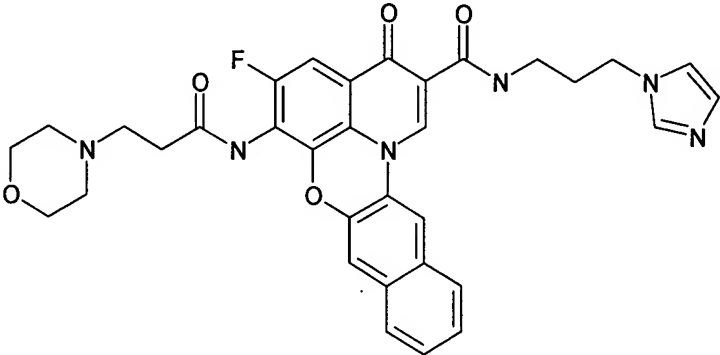
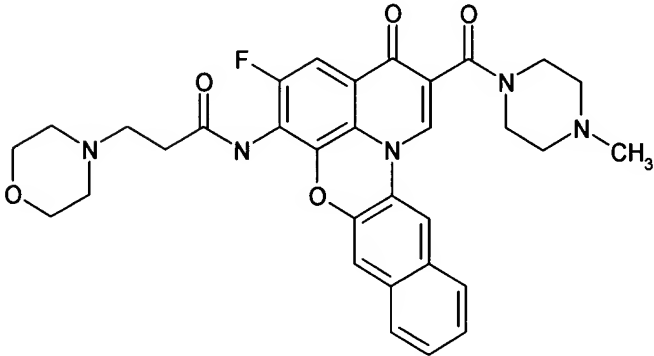
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1162			
1163			
1164			

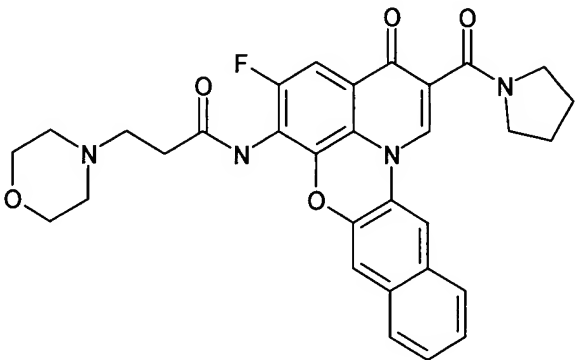
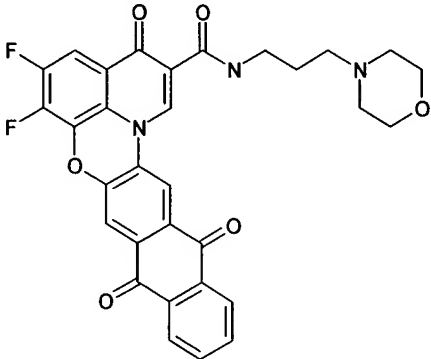
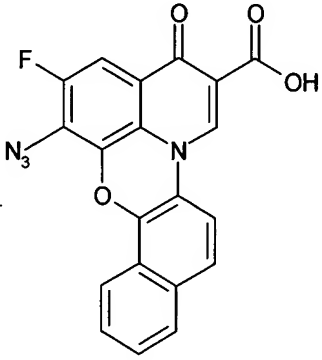
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1165			
1166			
1167			

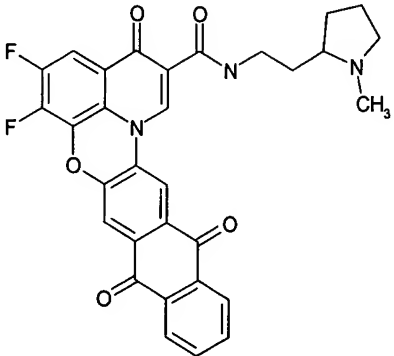
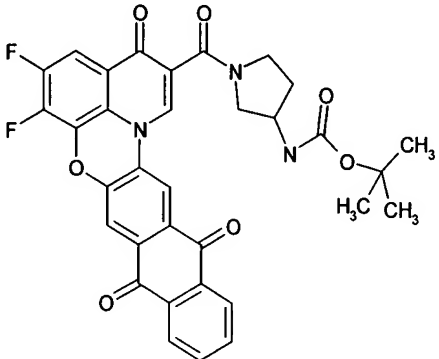
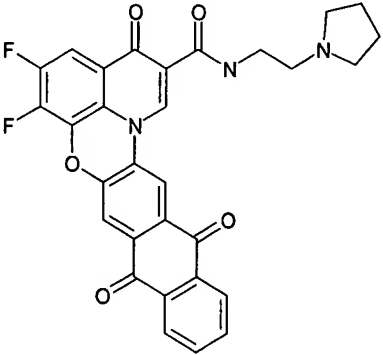
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1168			
1169			
1170			

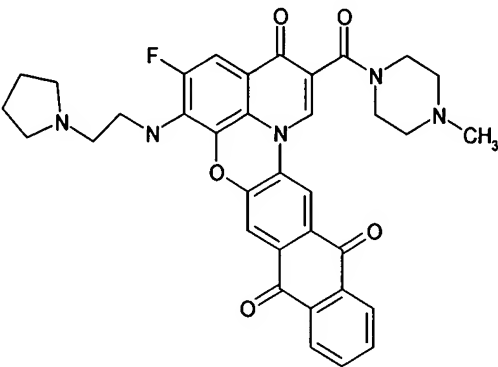
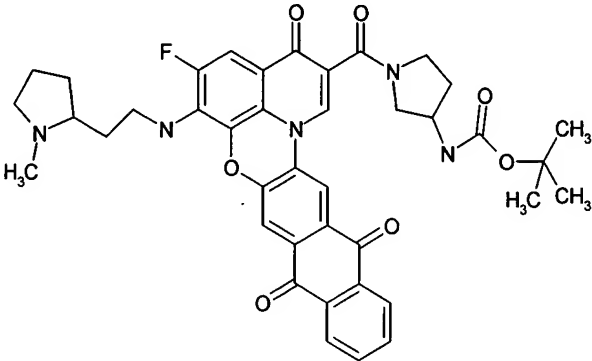
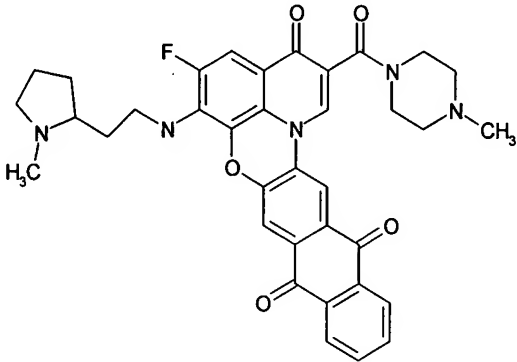


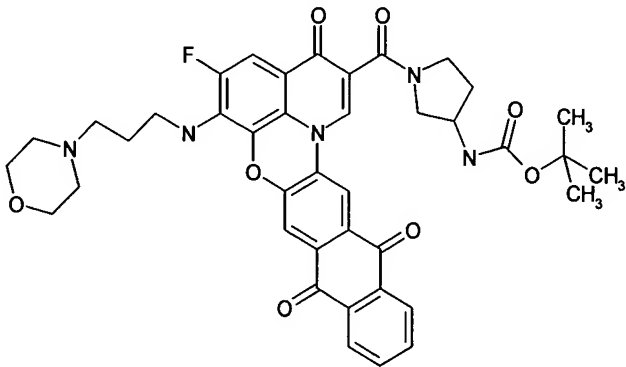
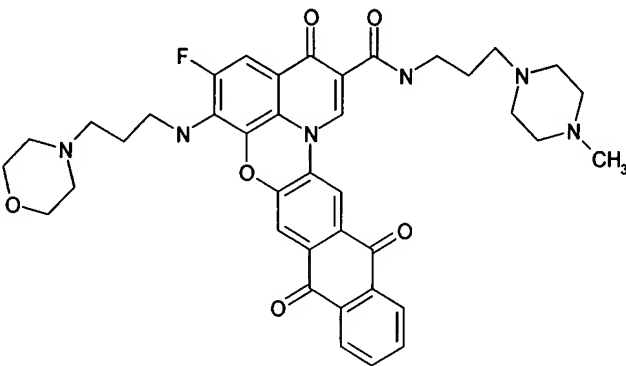
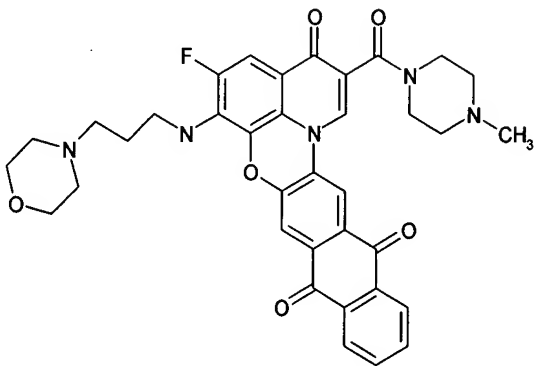
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1171			
1172			
1173			

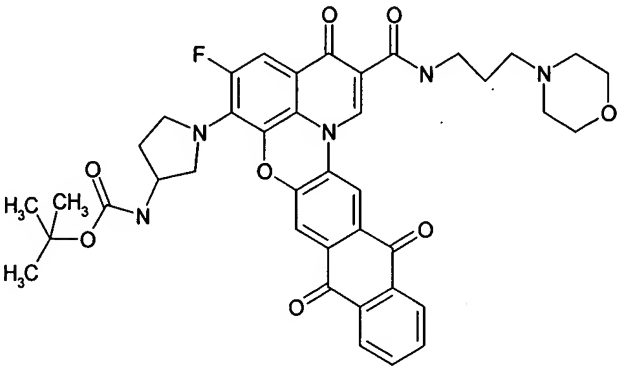
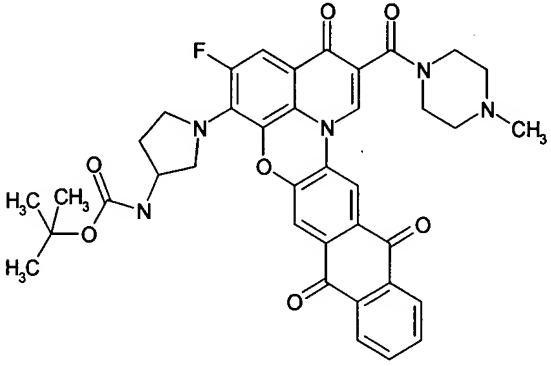
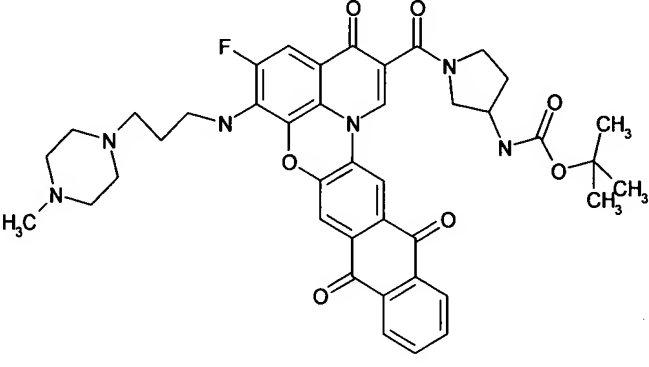
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1174			
1175			
1176			

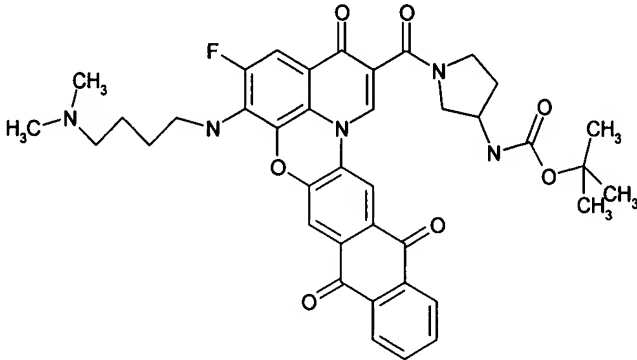
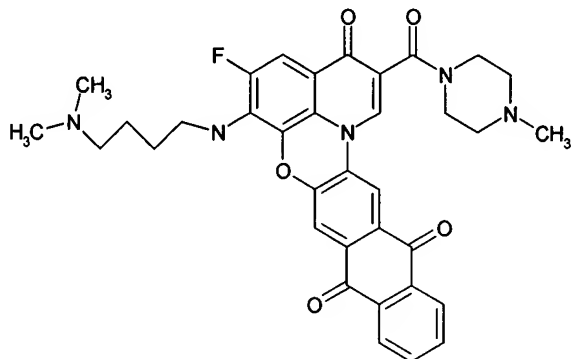
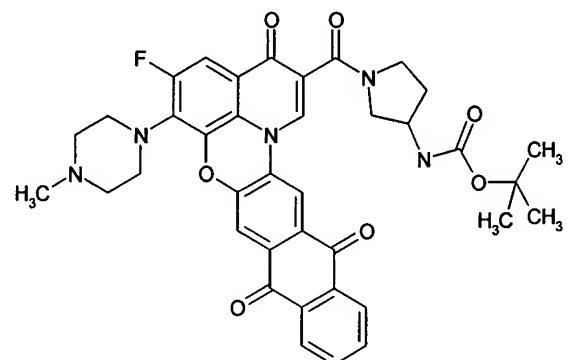
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1177			
1178			
1179			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1180			
1181			
1182			

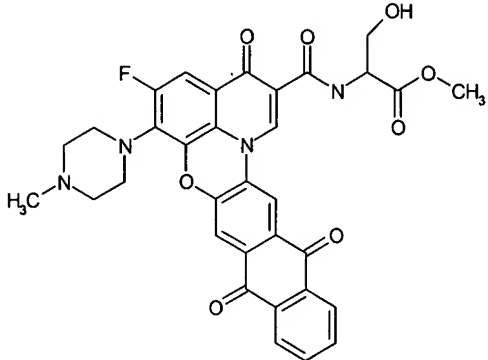
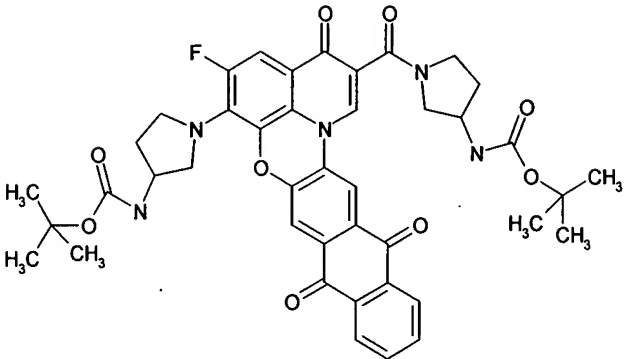
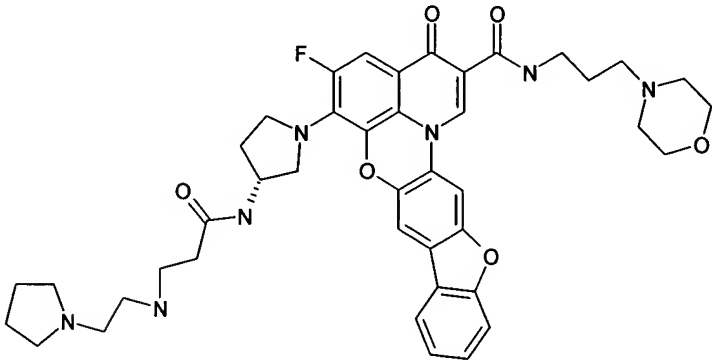
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1183			
1184			
1185			

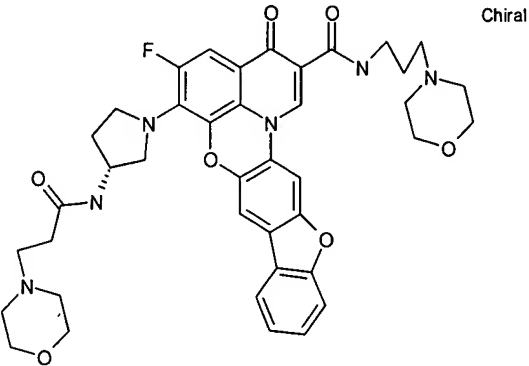
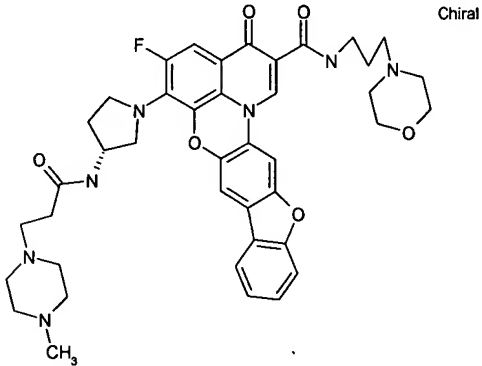
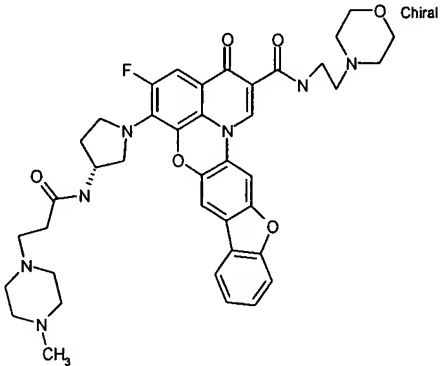
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1186			
1187			
1188			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1189			
1190			
1191			

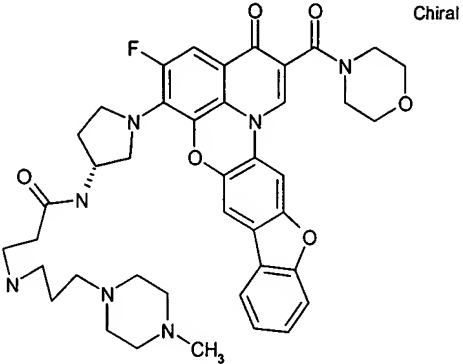
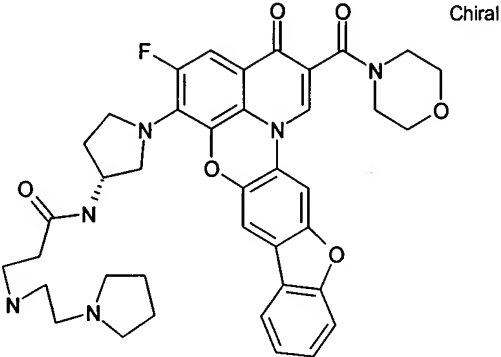
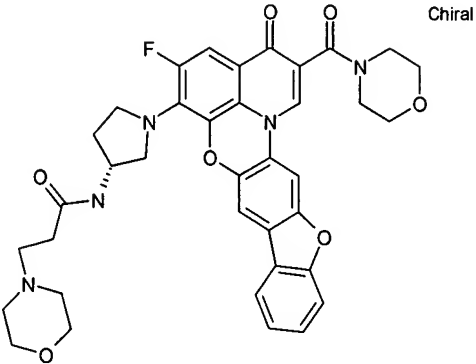
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1192			
1193			
1194			

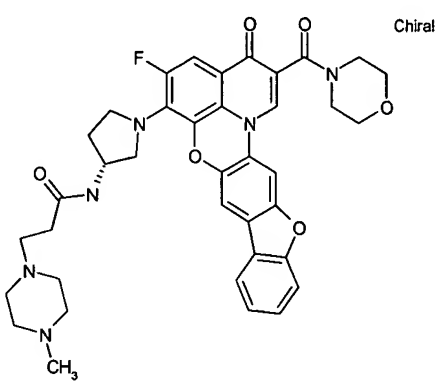
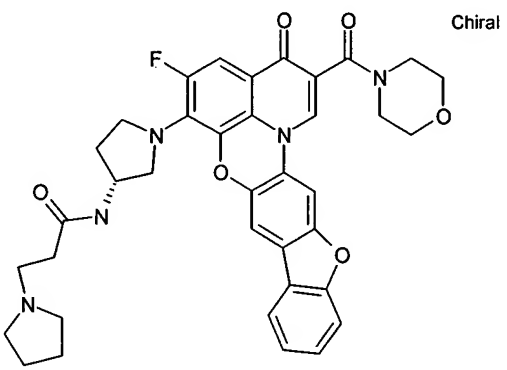
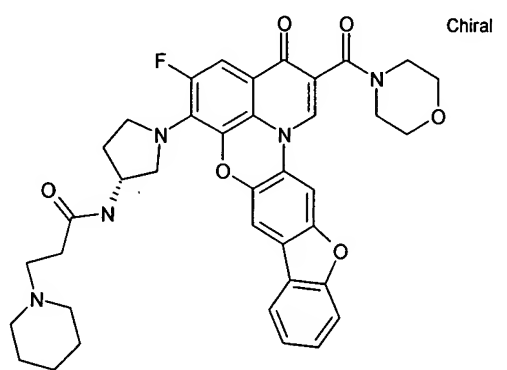


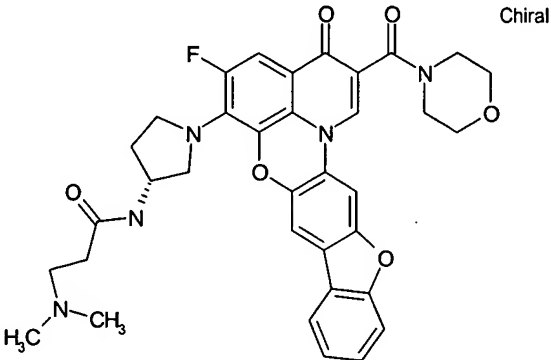
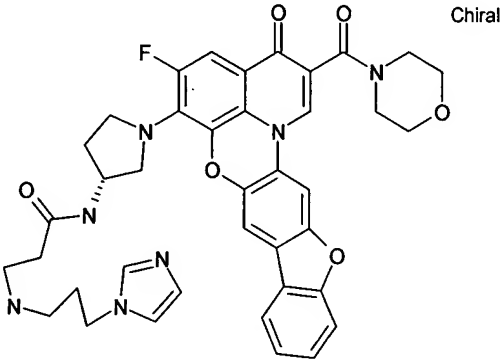
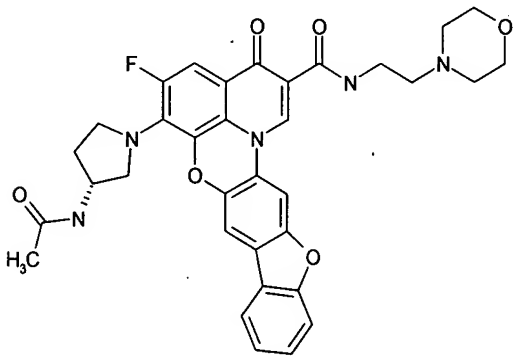
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1195			
1196			
1197			

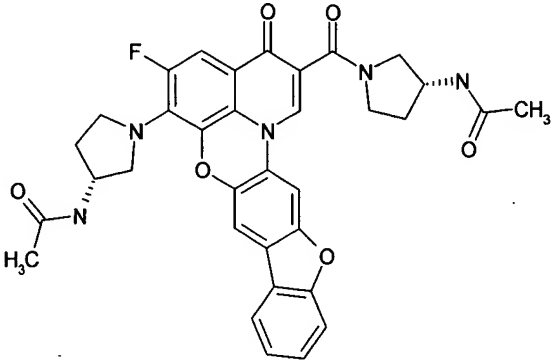
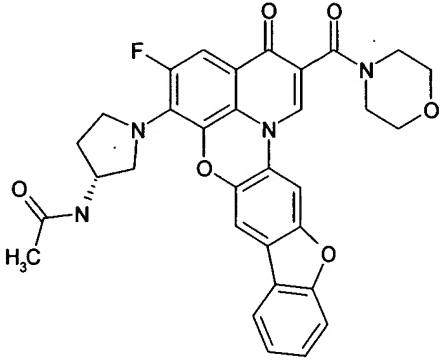
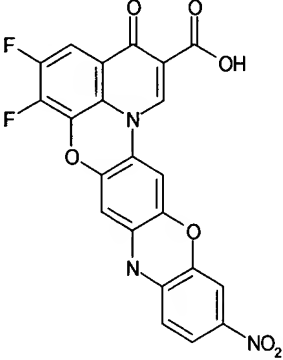
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1198	 <p style="text-align: right;">Chiral</p>		
1199	 <p style="text-align: right;">Chiral</p>		
1200	 <p style="text-align: right;">Chiral</p>		

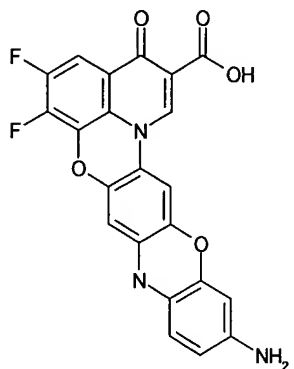
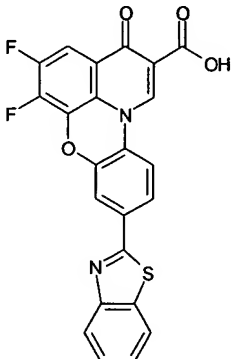
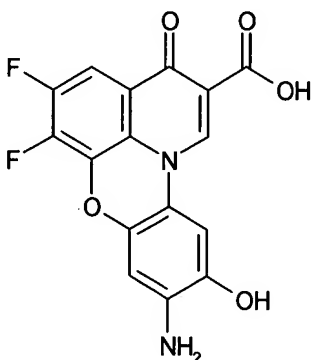
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1201	<p>Chiral</p>		
1202	<p>Chiral</p>		
1203	<p>Chiral</p>		

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1204	 <p>Chiral</p>		
1205	 <p>Chiral</p>		
1206	 <p>Chiral</p>		

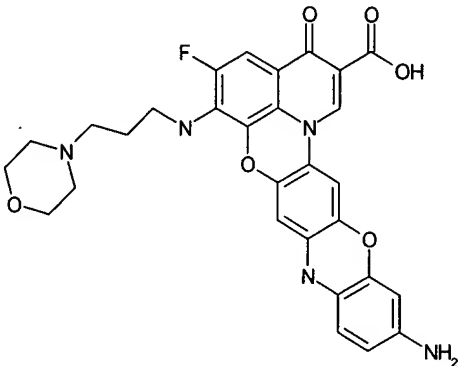
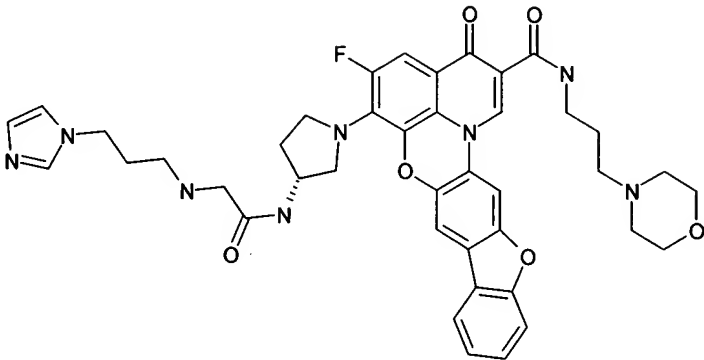
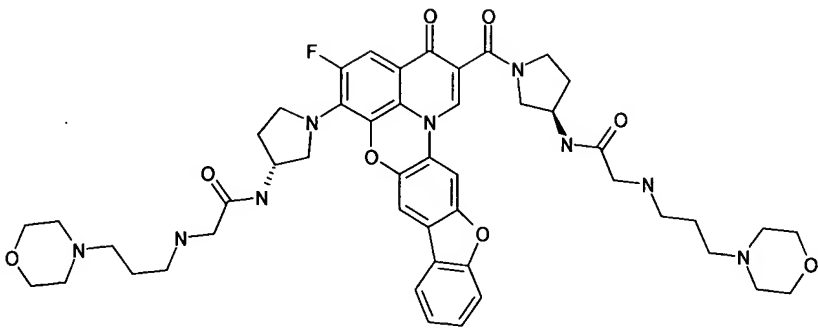
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1207			
1208			
1209			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1210			
1211			
1212			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1213			
1214			
1215			

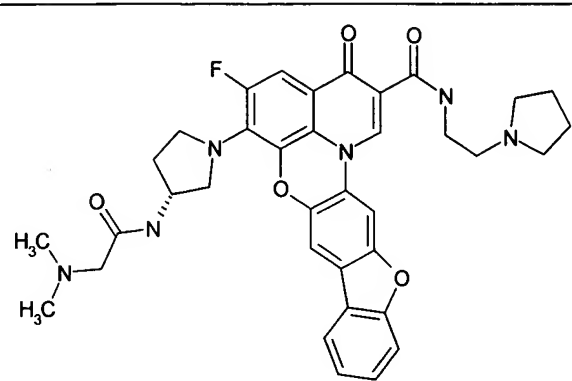
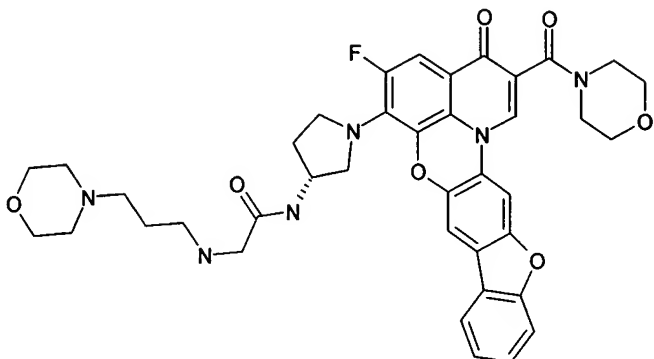
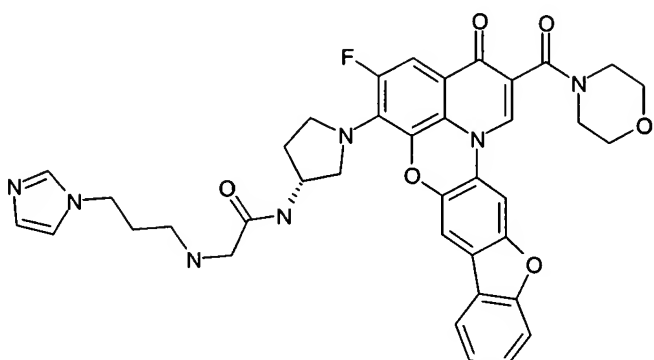
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1216			
1217			
1218			

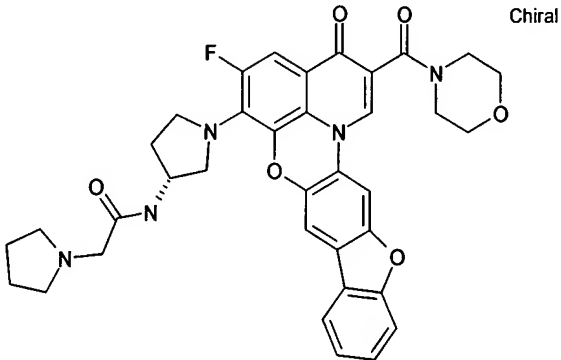
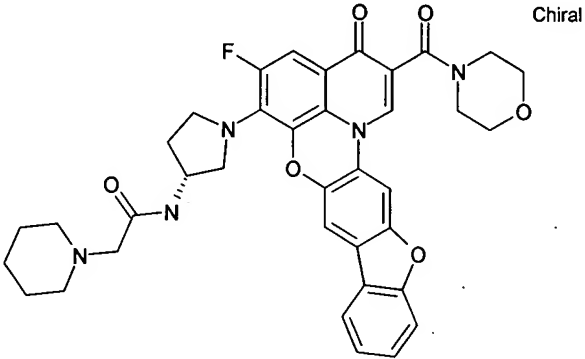
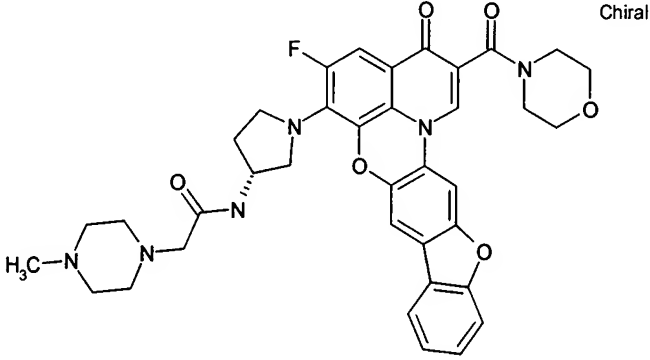


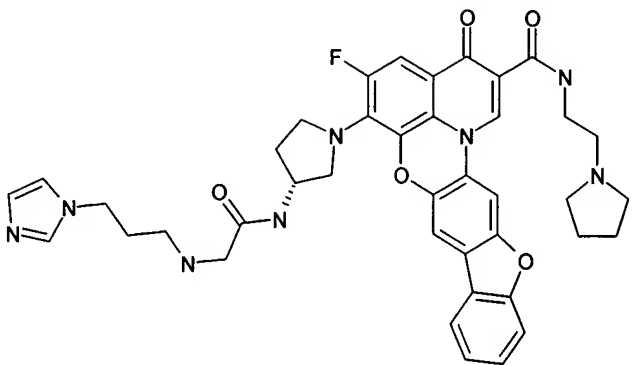
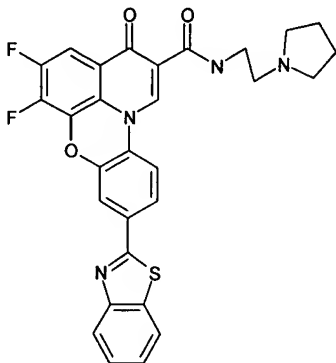
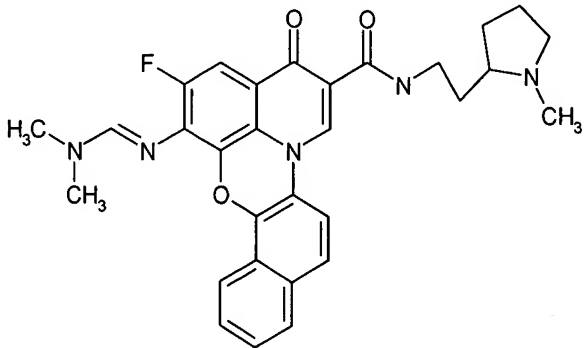
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1219			
1220	 Chiral		
1221	 Chiral		

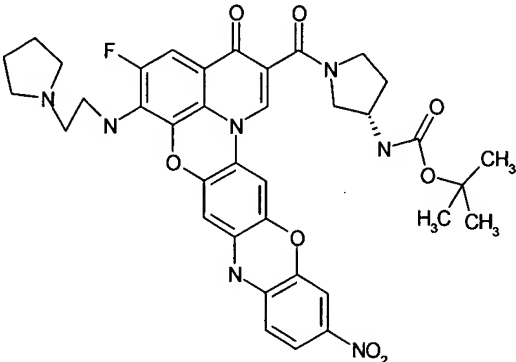
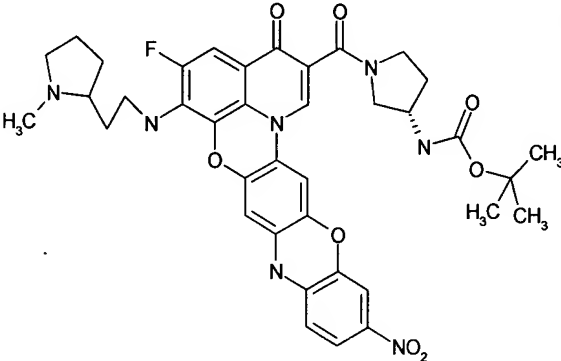
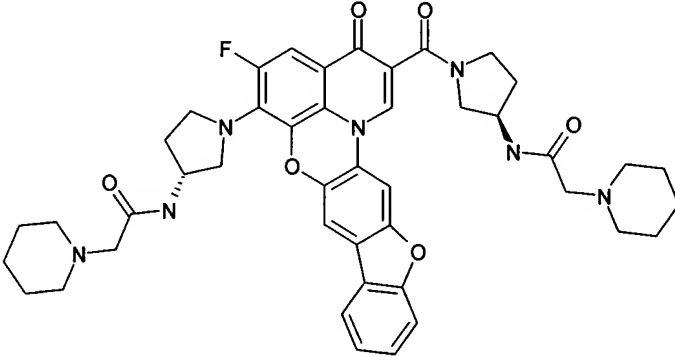


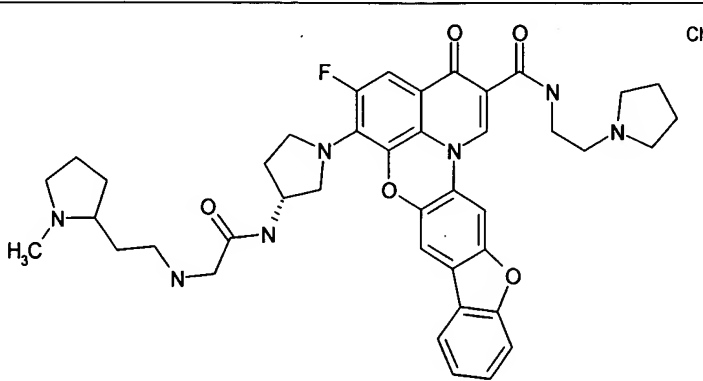
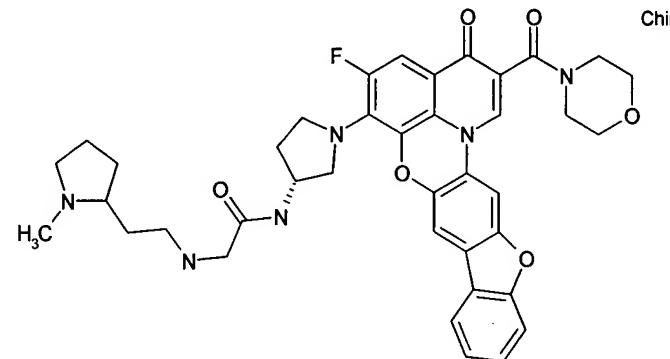
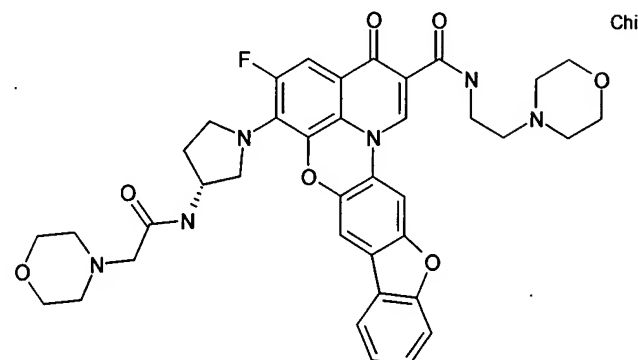
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1225	<p>Chiral</p>		
1226	<p>Chiral</p>		
1227	<p>Chiral</p>		

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1228	 <p>Chiral</p>		
1229	 <p>Chiral</p>		
1230	 <p>Chiral</p>		

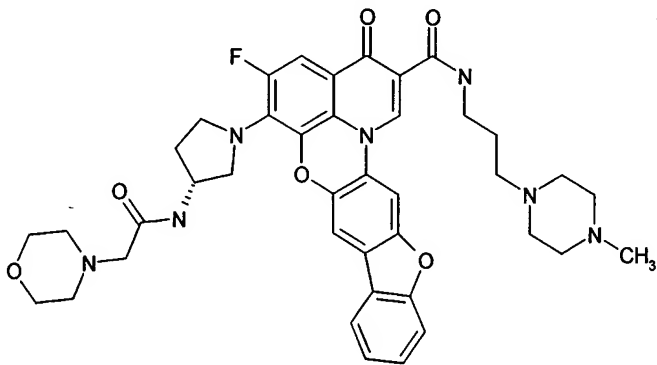
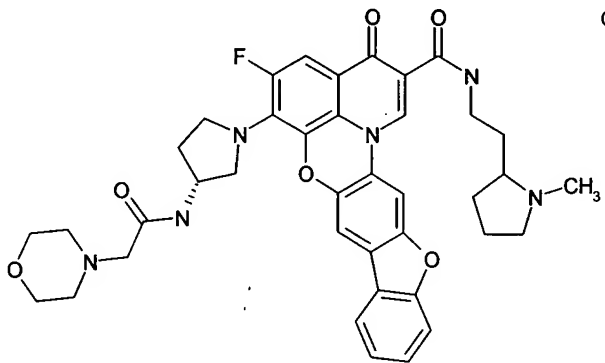
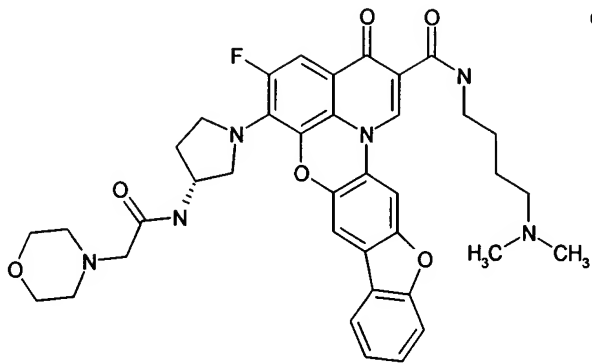
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1231	 <p>Chiral</p>		
1232	 <p>Chiral</p>		
1233	 <p>Chiral</p>		

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1234	 <p style="text-align: right;">Chiral</p>		
1235			
1236			

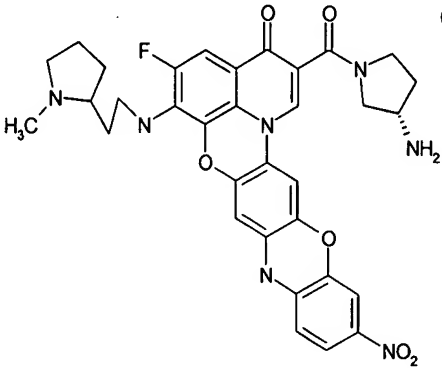
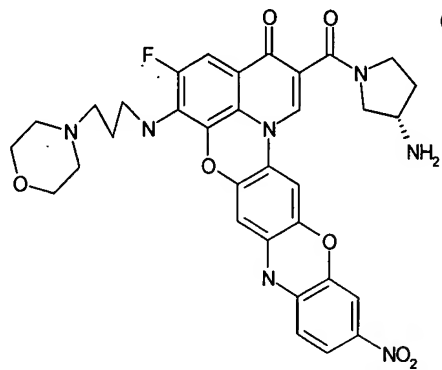
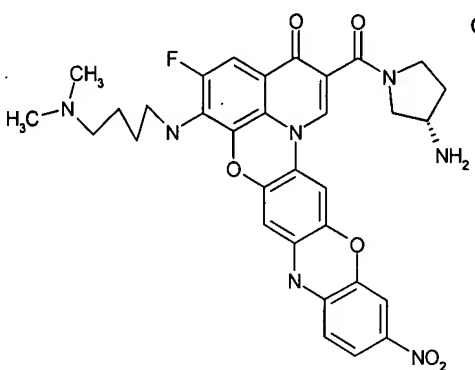
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1237	 <p>Chiral</p>		
1238	 <p>Chiral</p>		
1239	 <p>Chiral</p>		

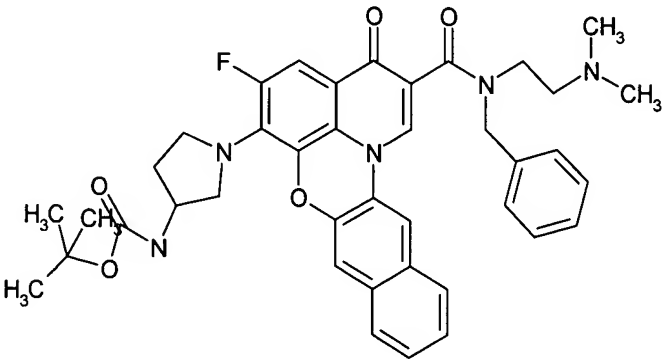
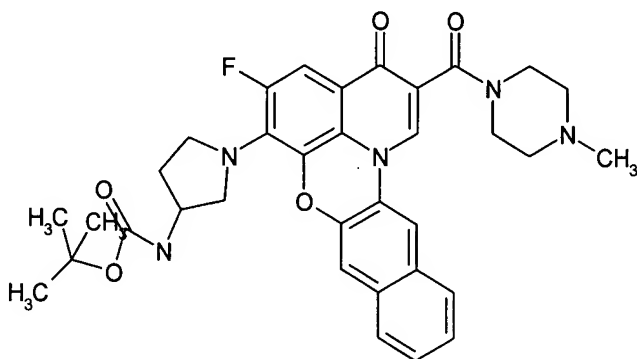
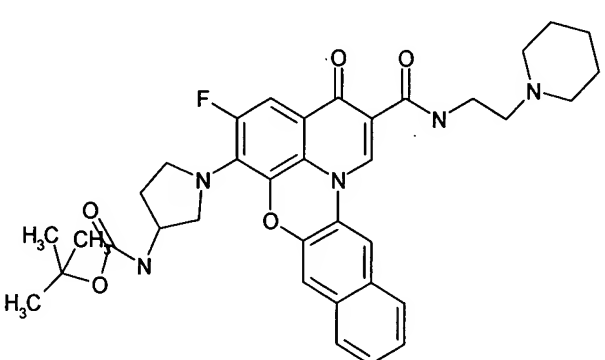
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1240	<p>Chiral</p> 		
1241	<p>Chiral</p> 		
1242	<p>Chiral</p> 		

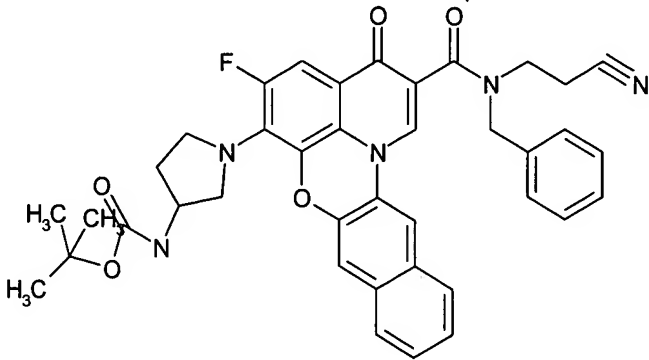
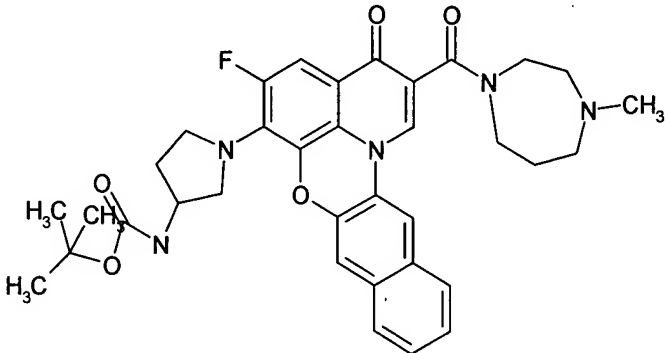
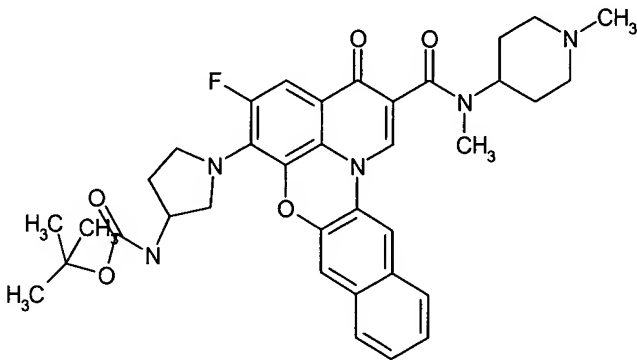


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1243	<p>Chiral</p> 		
1244	<p>Chiral</p> 		
1245	<p>Chiral</p> 		

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1246	<p>Chiral</p>		
1247	<p>Chiral</p>		
1248	<p>Chiral</p>		

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1249	 <p>Chiral</p>		
1250	 <p>Chiral</p>		
1251	 <p>Chiral</p>		

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1252			
1253			
1254			

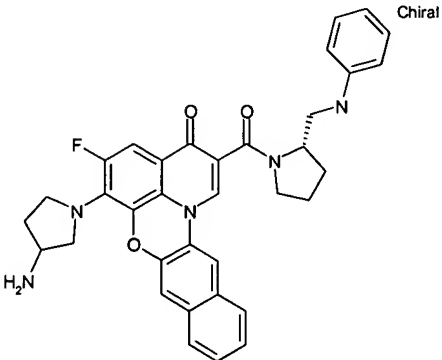
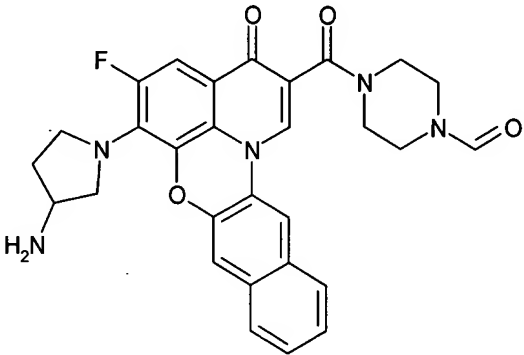
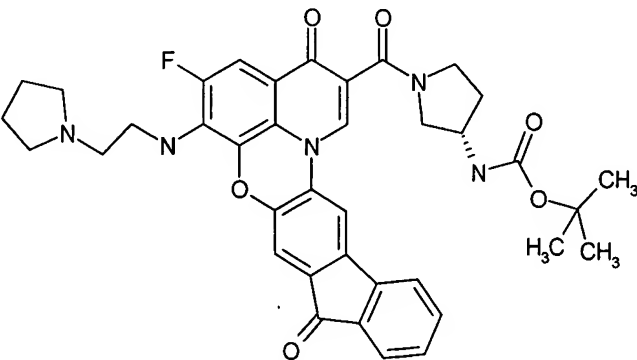
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1255			
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1257			

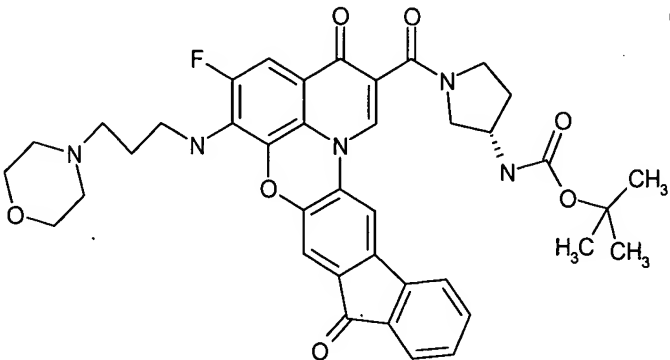
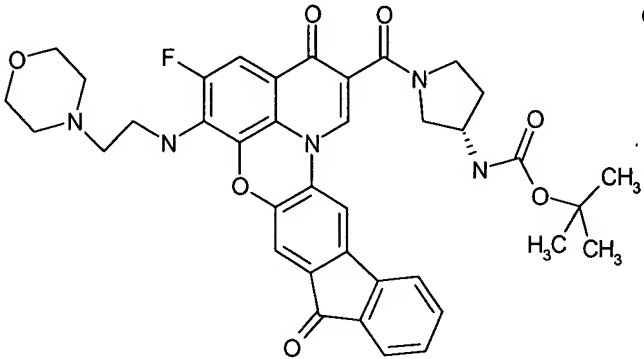
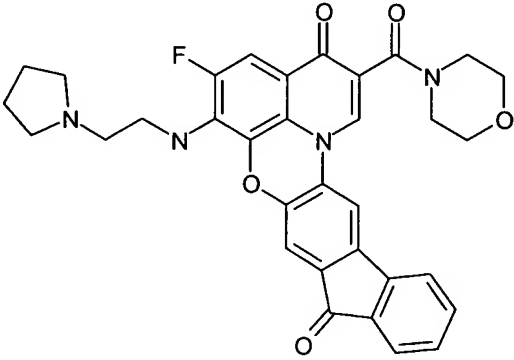
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1259			
1260			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1263			

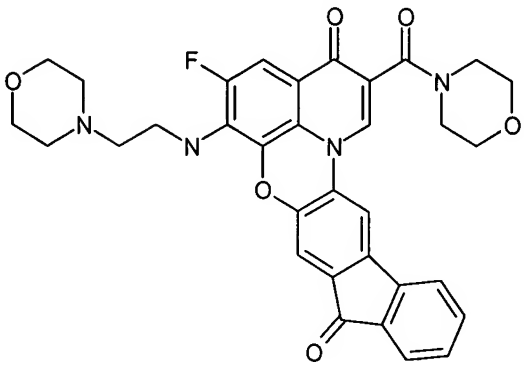
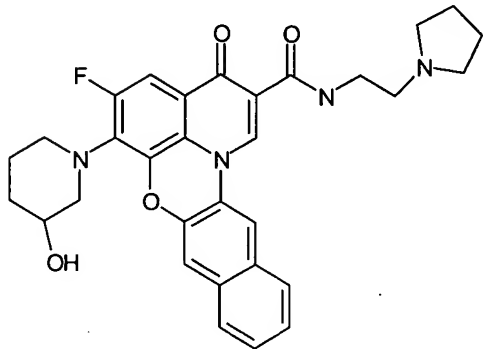
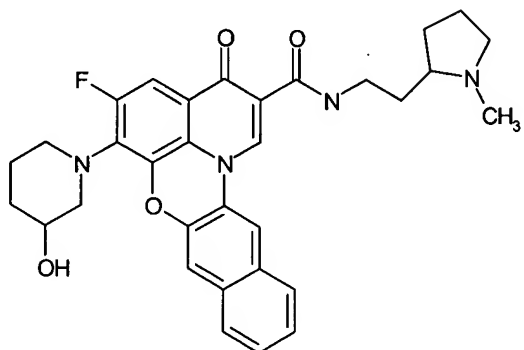
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1266			

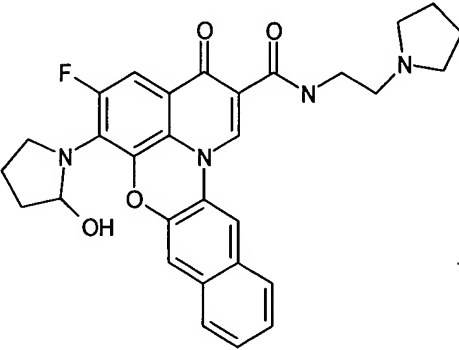
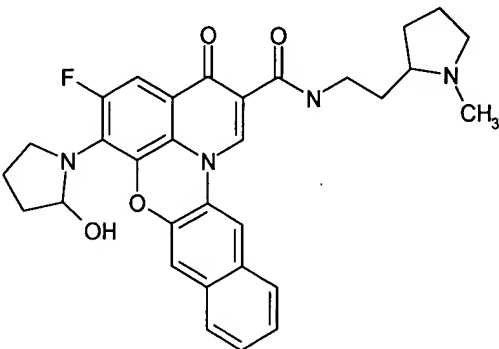
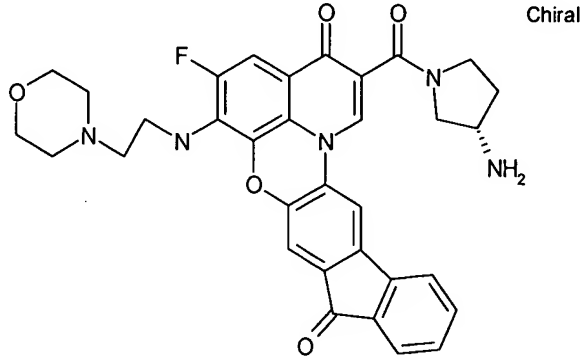


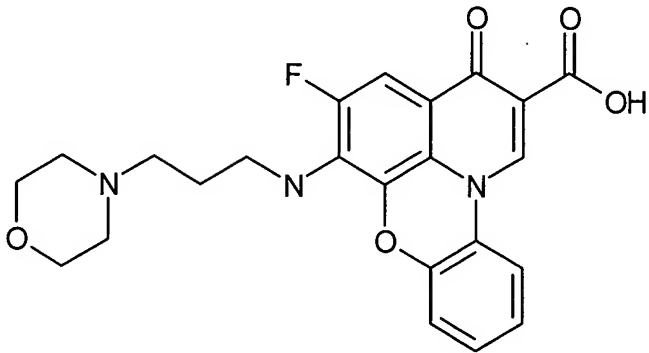
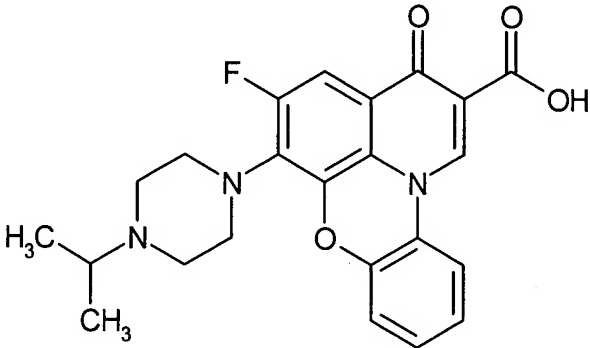
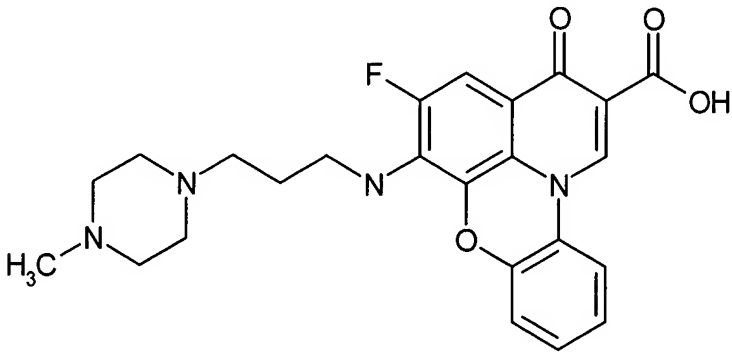
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1268			
1269			

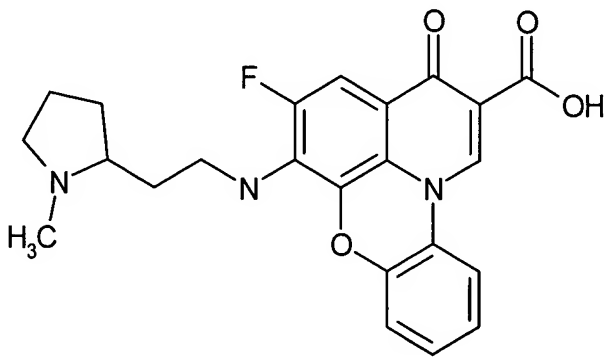
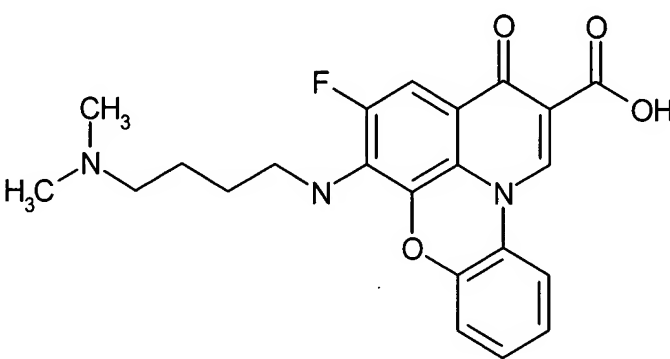
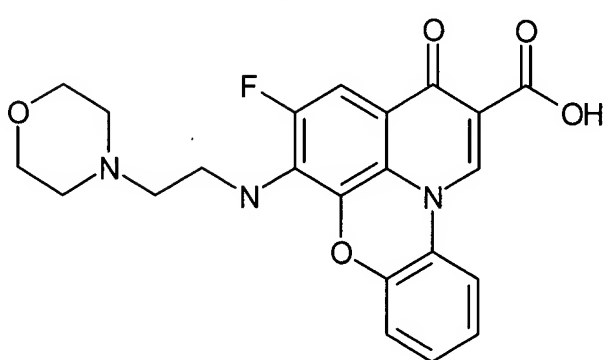
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1270	<p>Chiral</p> 		
1271	<p>Chiral</p> 		
1272			

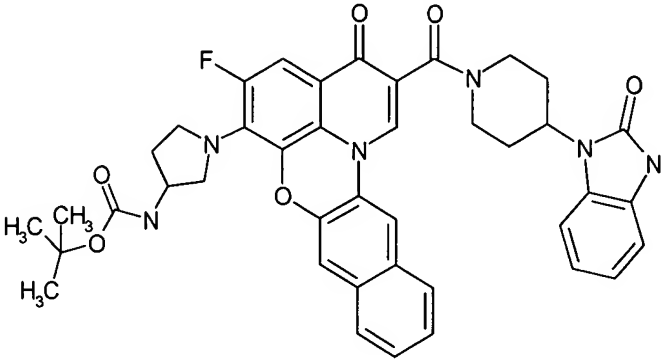
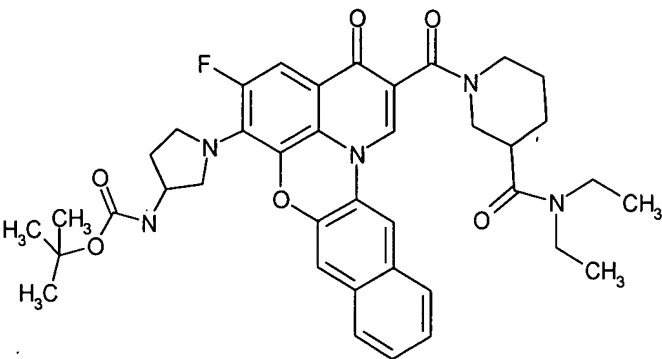
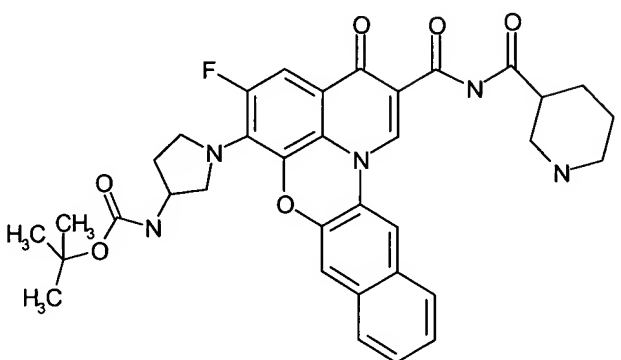
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1274			
1275			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1276			
1277			
1278			

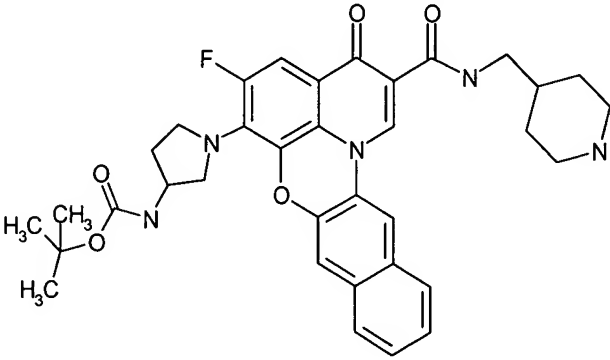
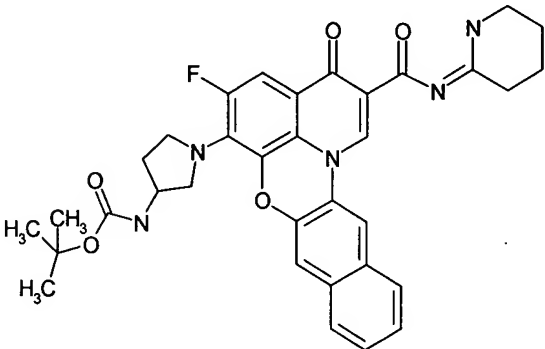
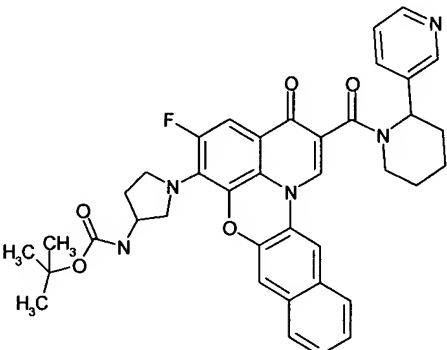
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1279			
1280			
1281			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1282			
1283			
1284			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1286			
1287			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1288			
1289			
1290			

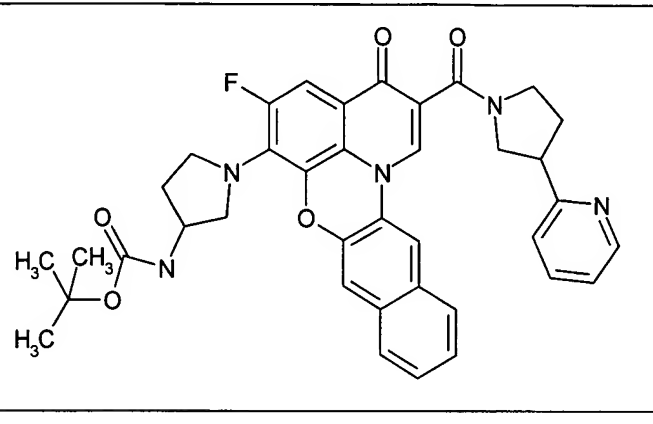
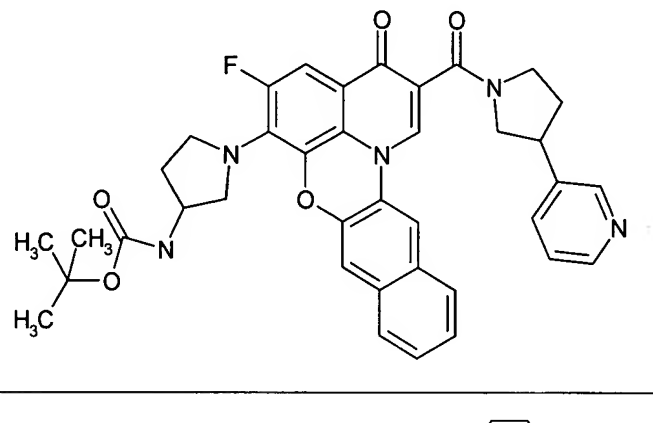
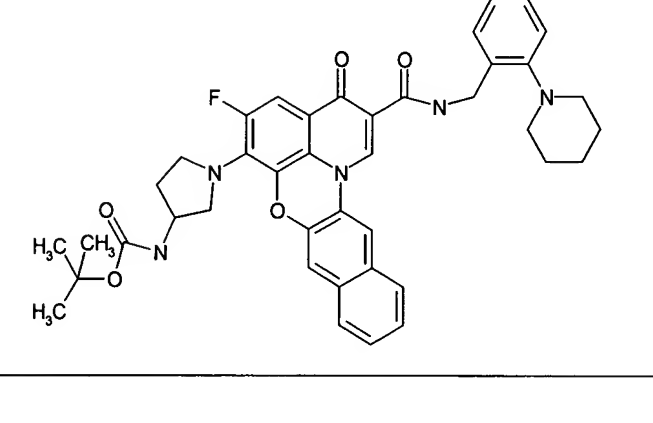


	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1292			
1293			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1295			
1296			

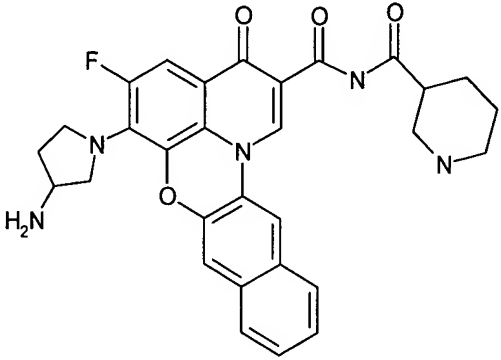
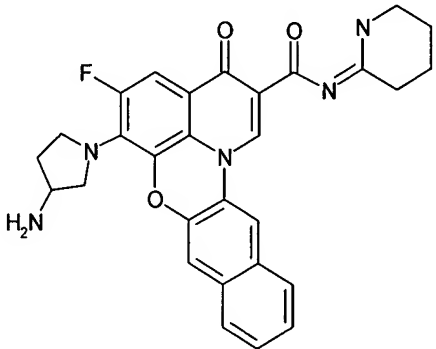
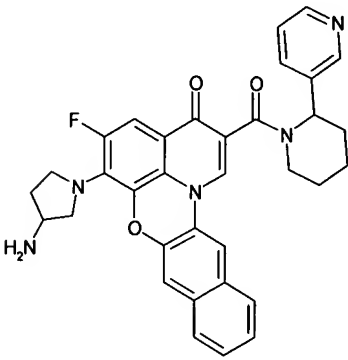
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1298			
1299			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1300			
1301			
1302			

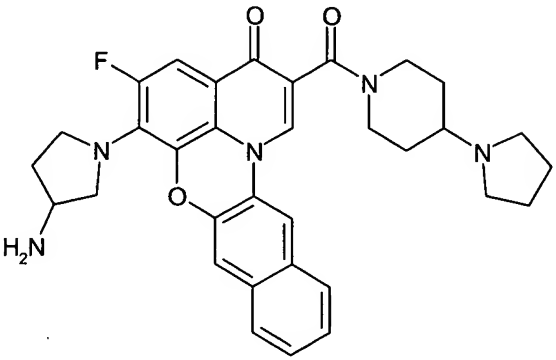
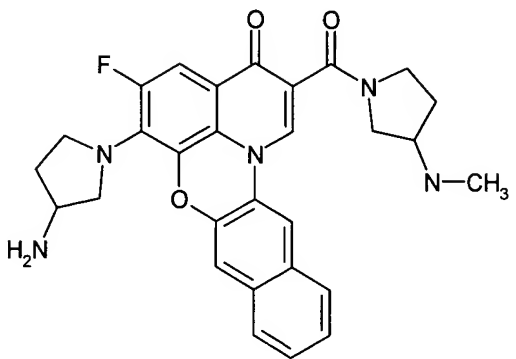
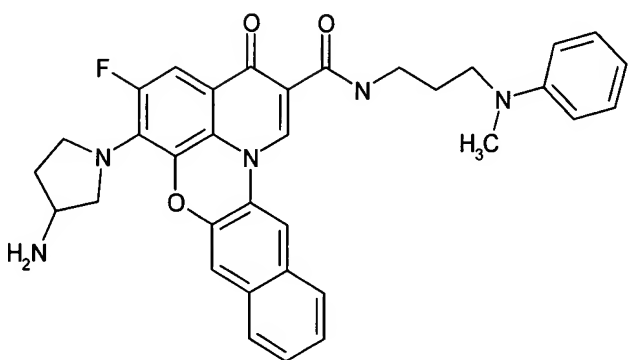
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1303			
1304			
1305			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1306			
1307			
1308			

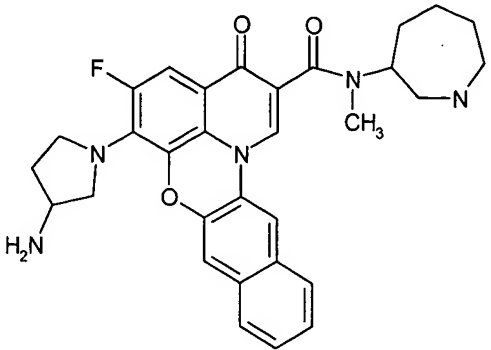
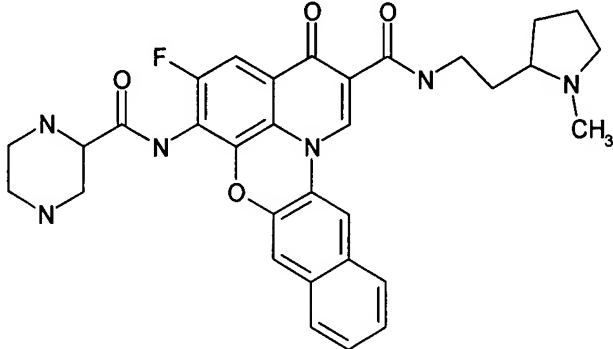
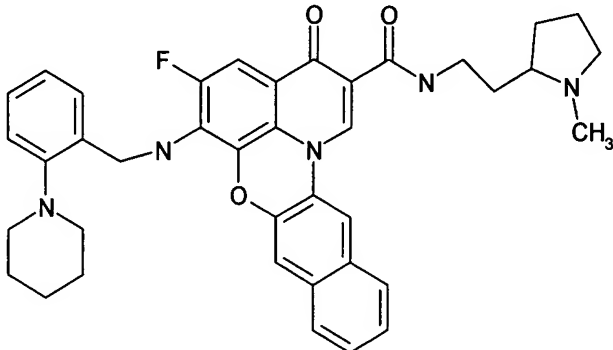
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1310			
1311			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1312			
1313			
1314			

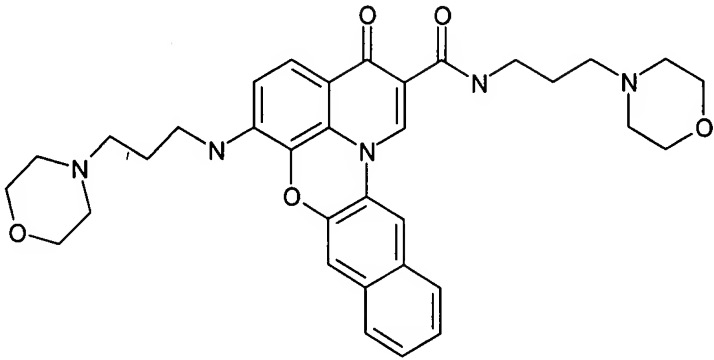
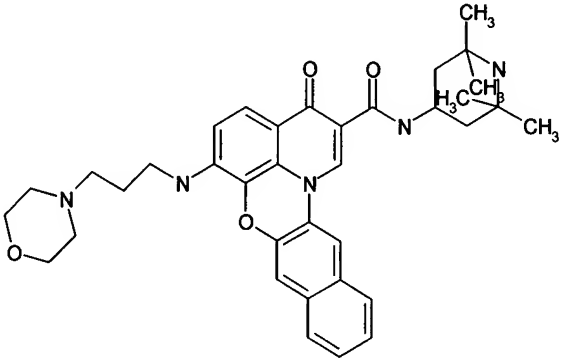
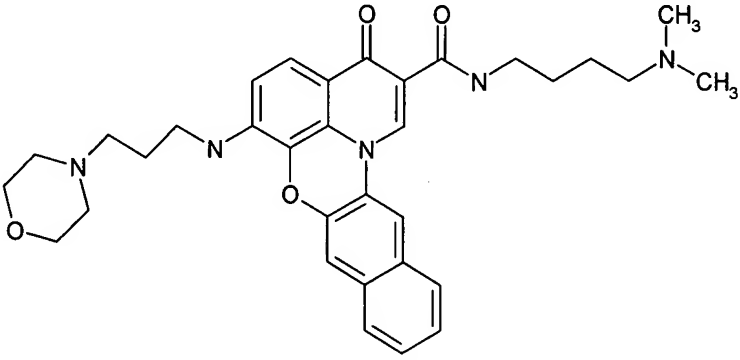


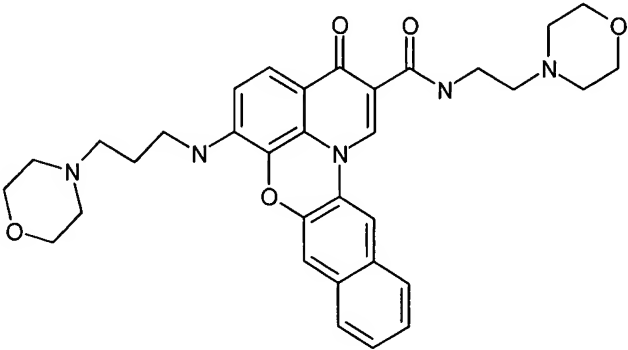
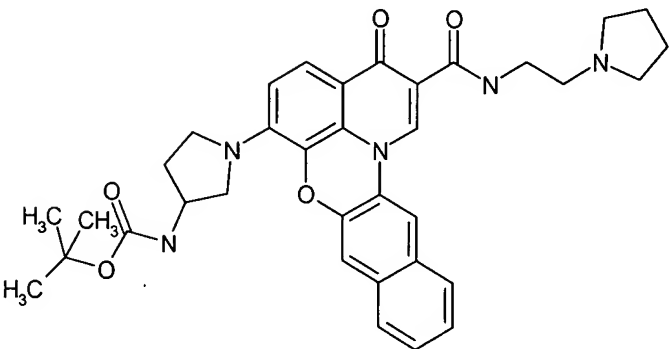
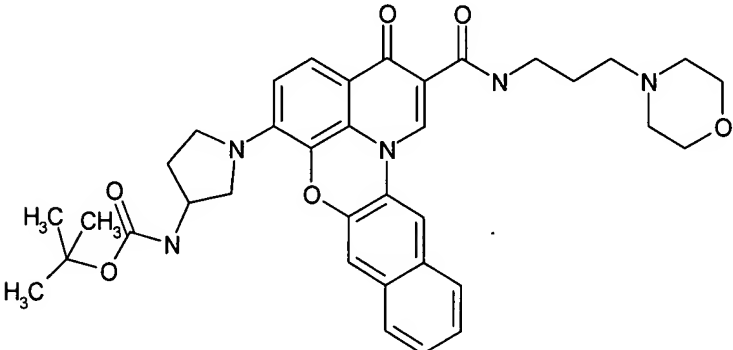
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1316			
1317			

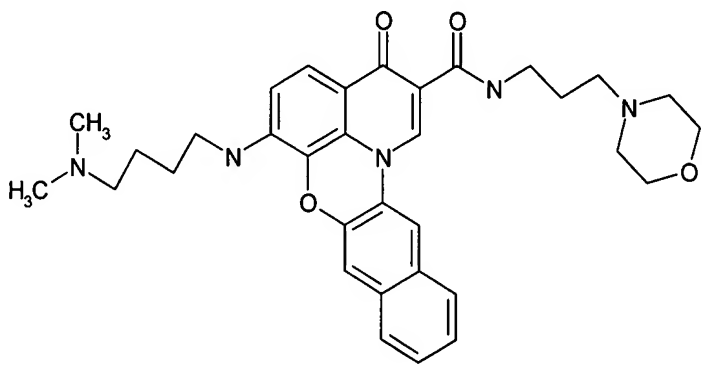
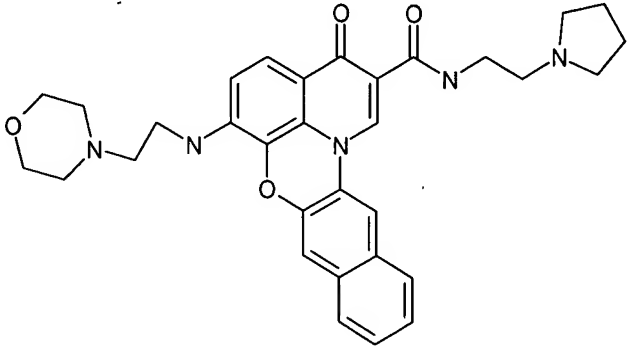
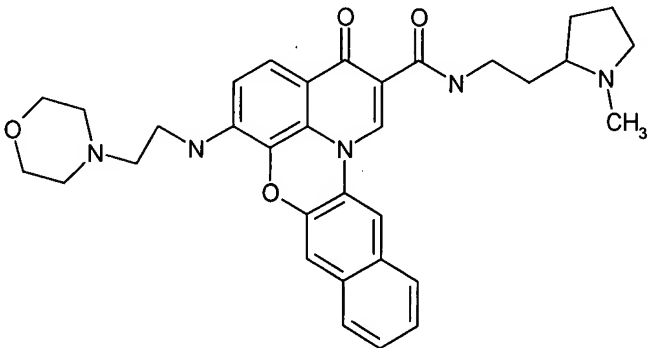
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1319			
1320			

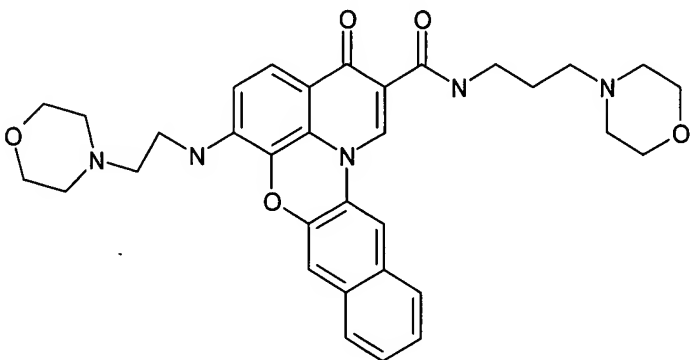
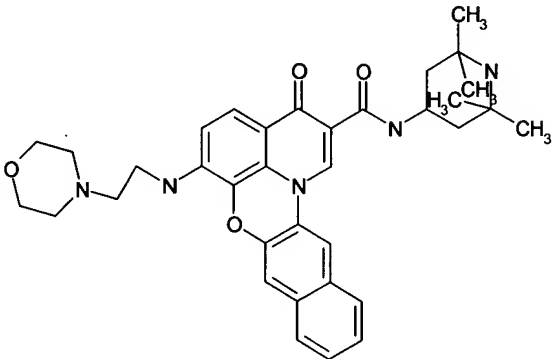
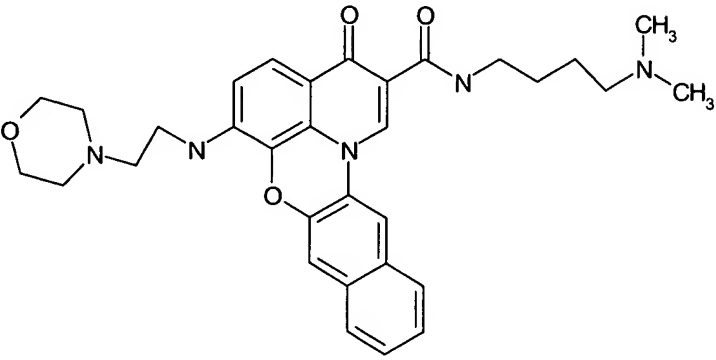
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1321			
1322			
1323			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1324			
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1326			

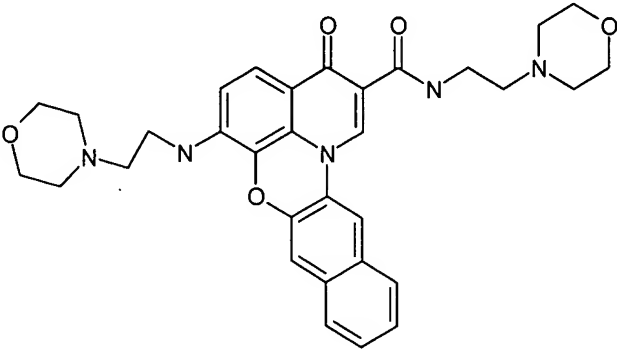
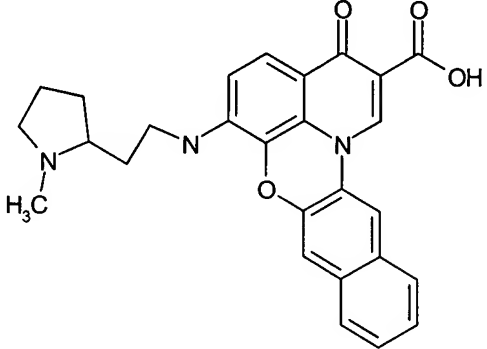
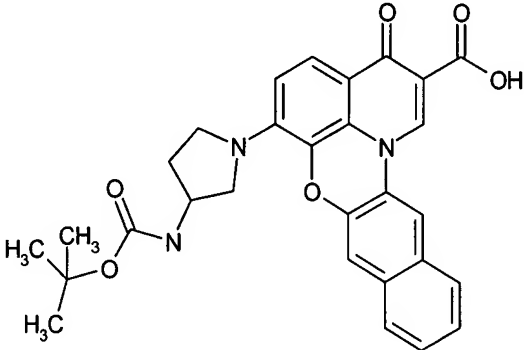
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1329			

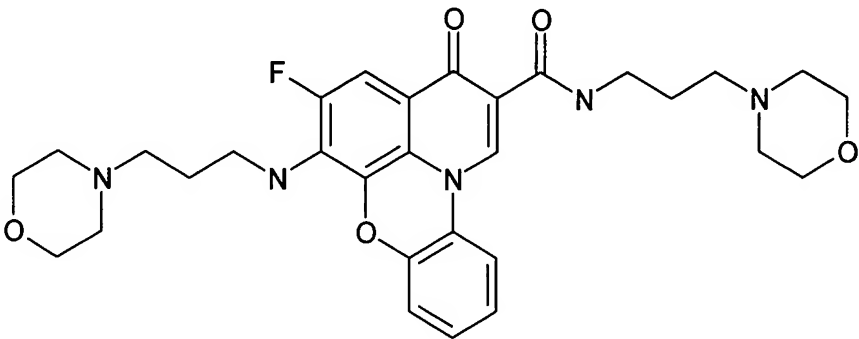
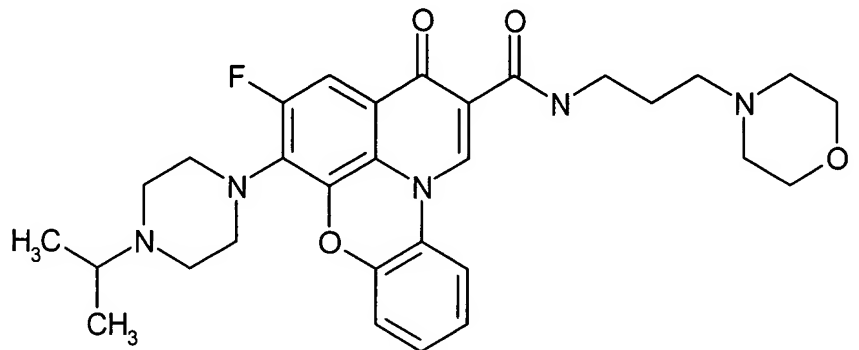
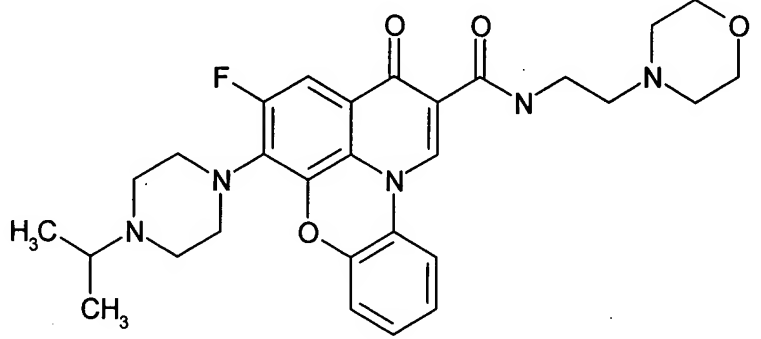
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1331			
1332			

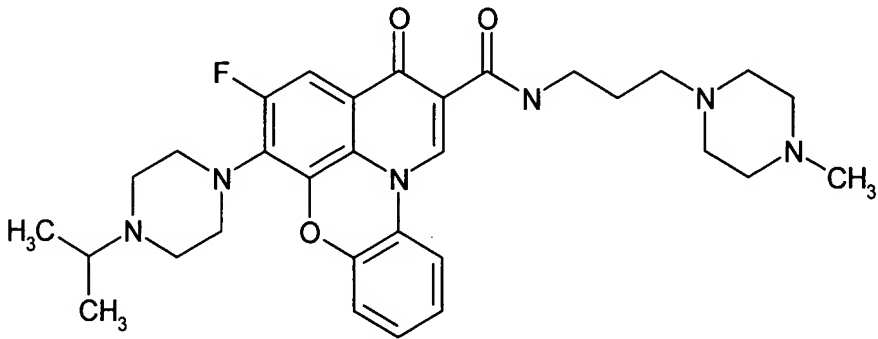
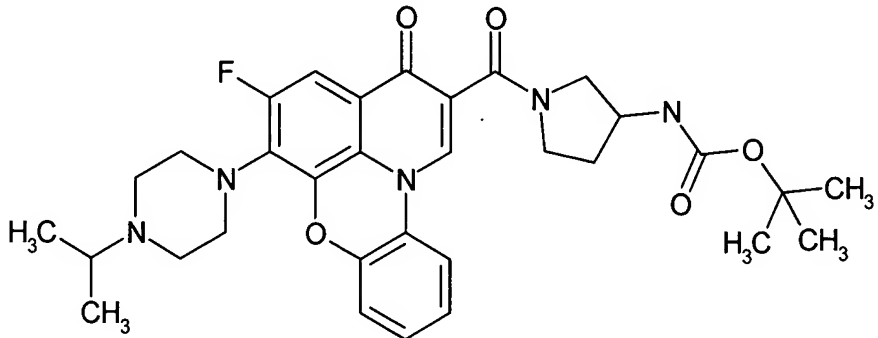
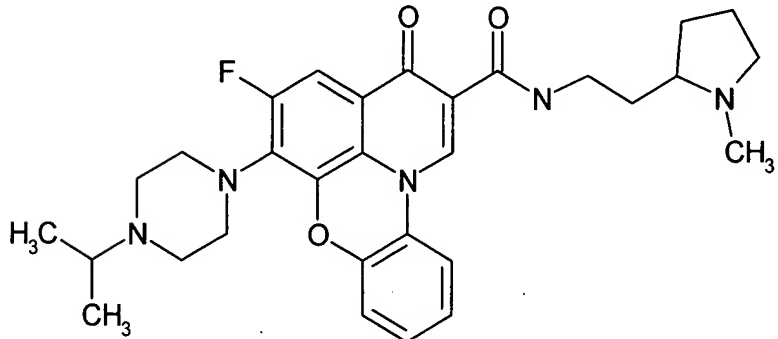
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1334			
1335			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1337			
1338			

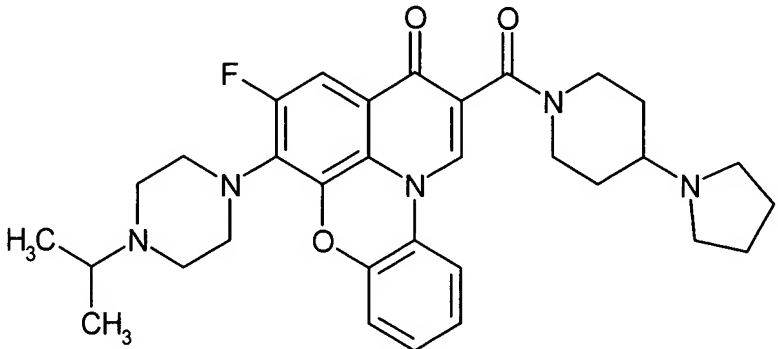
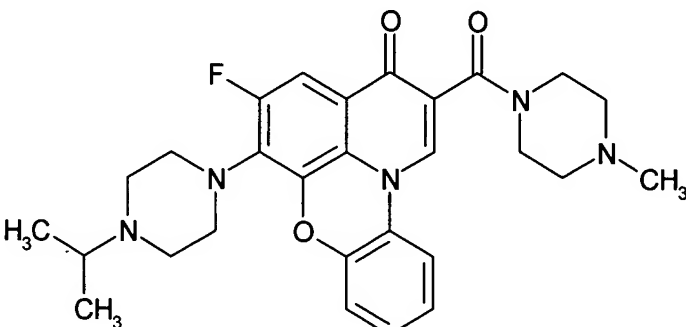
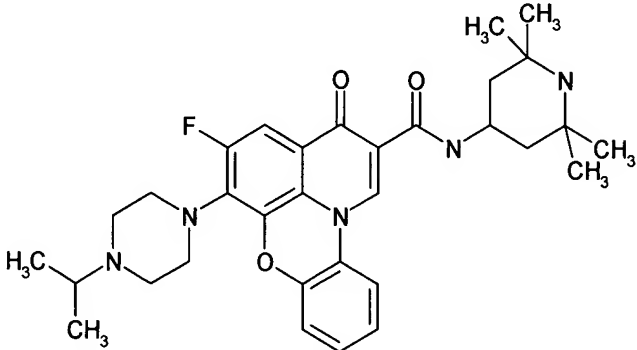
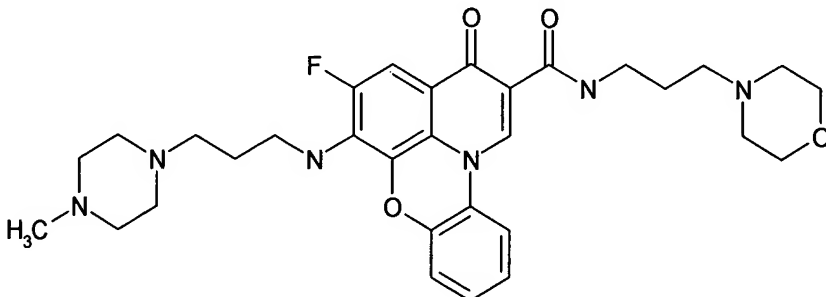


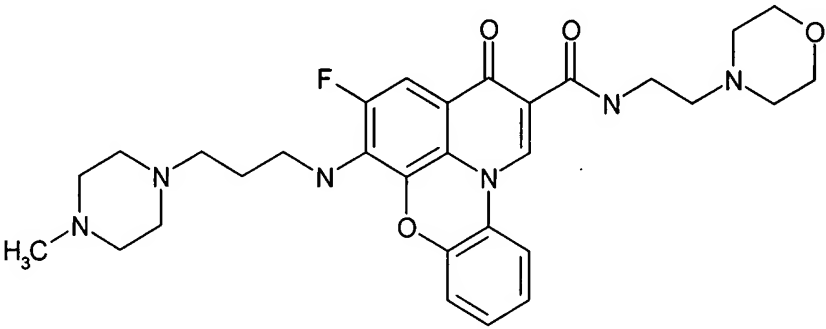
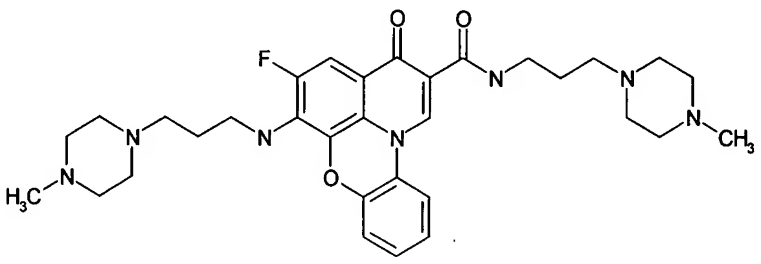
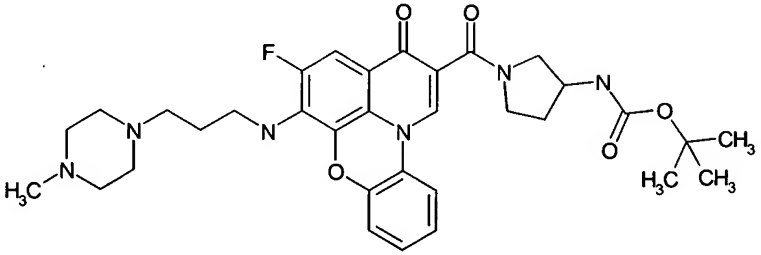
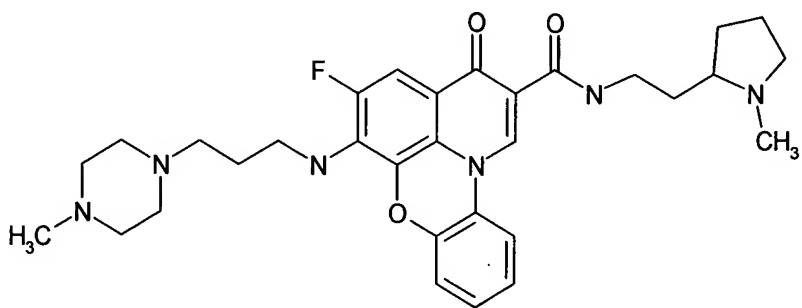
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1340			
1341			

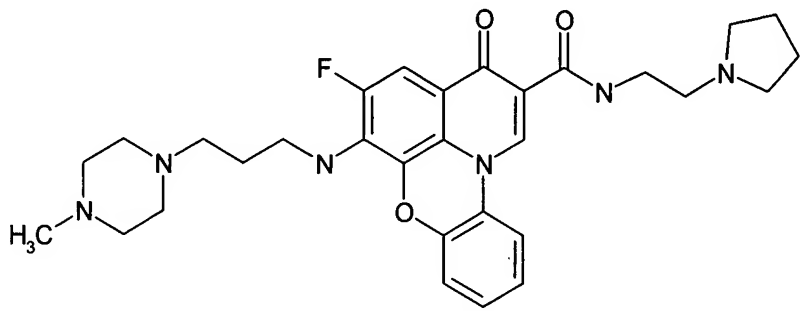
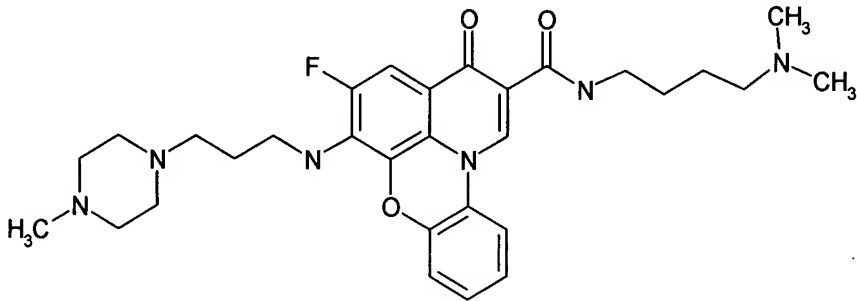
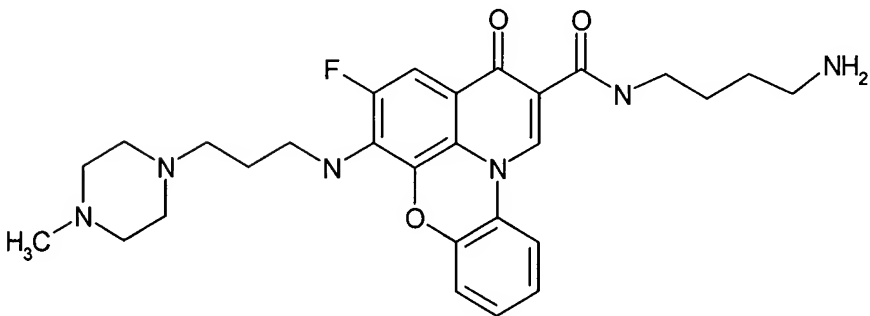
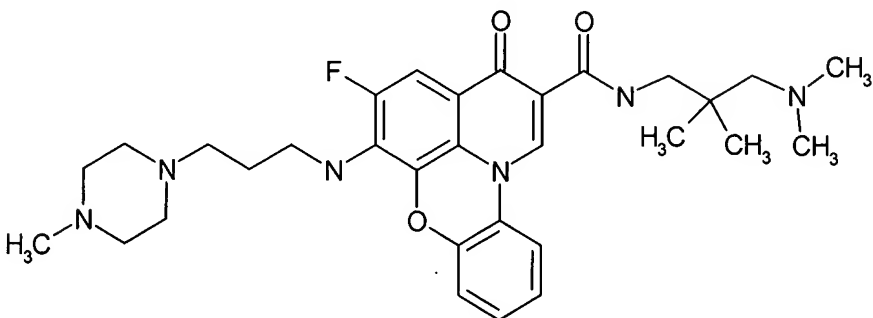
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1343			
1344			

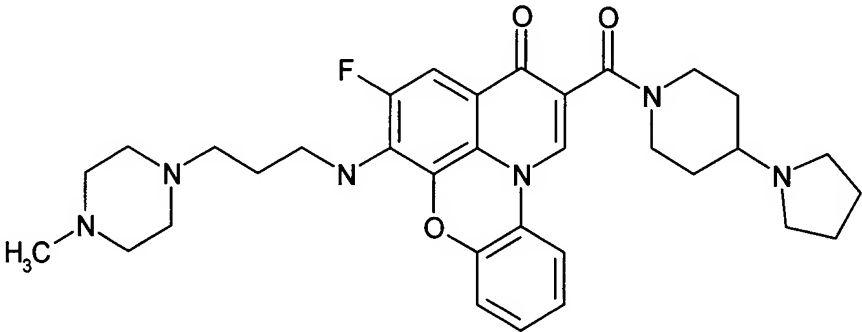
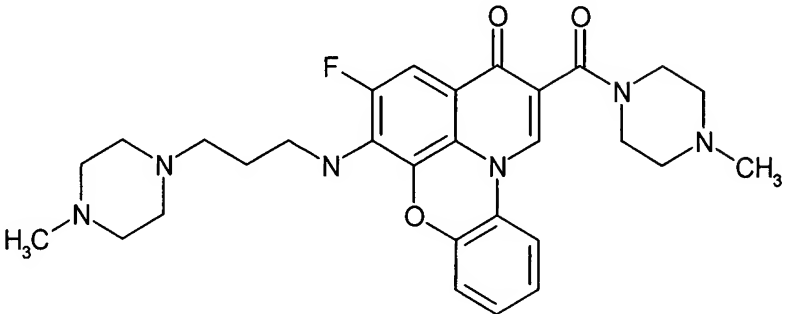
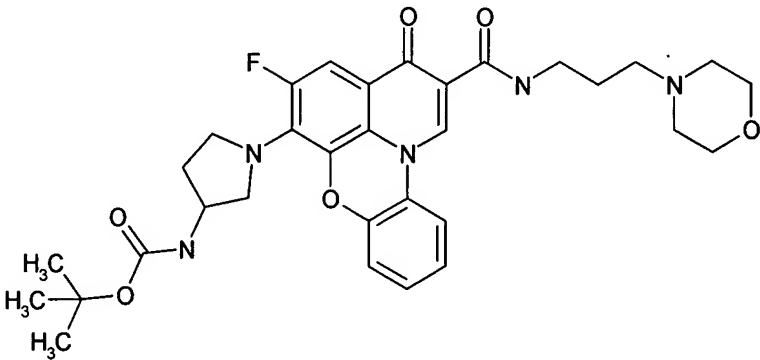
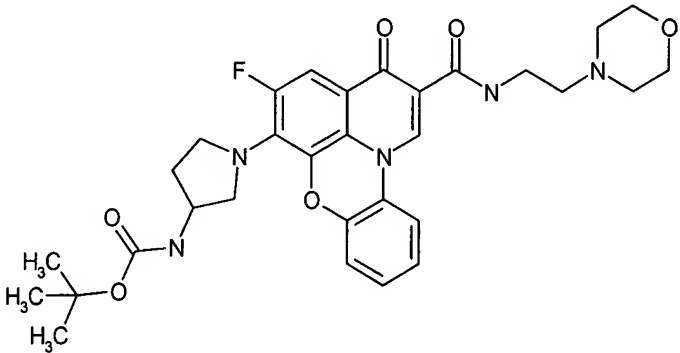
	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1345			
1346			
1347			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1348			
1349			
1350			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1351			
1352			
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1354			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1356			
1357			
1358			

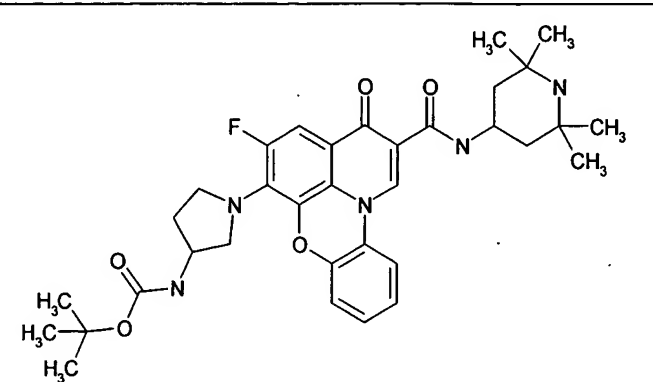
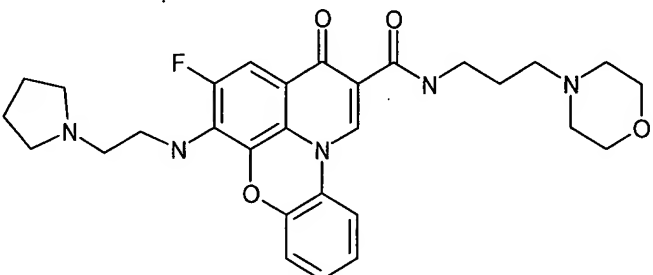
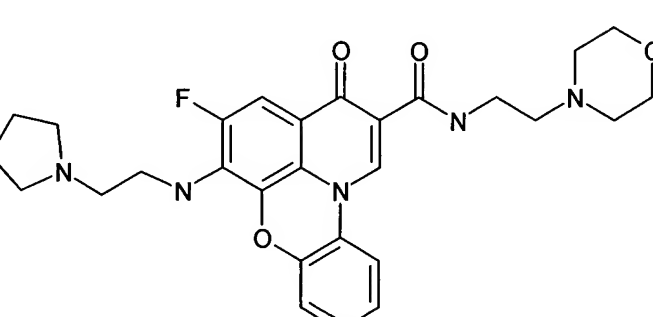
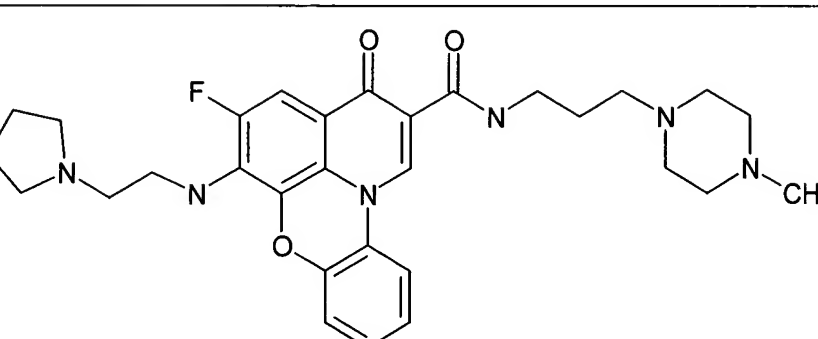
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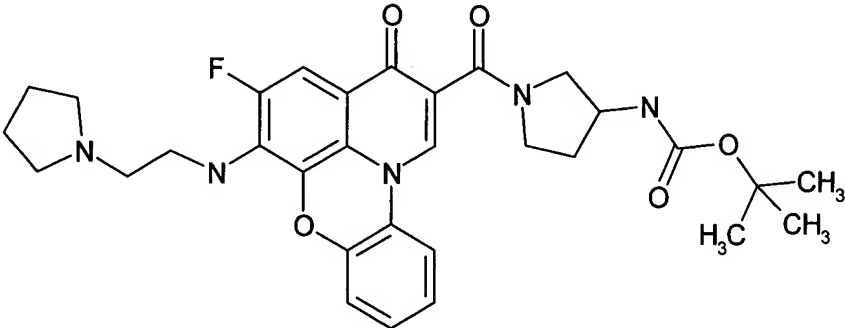
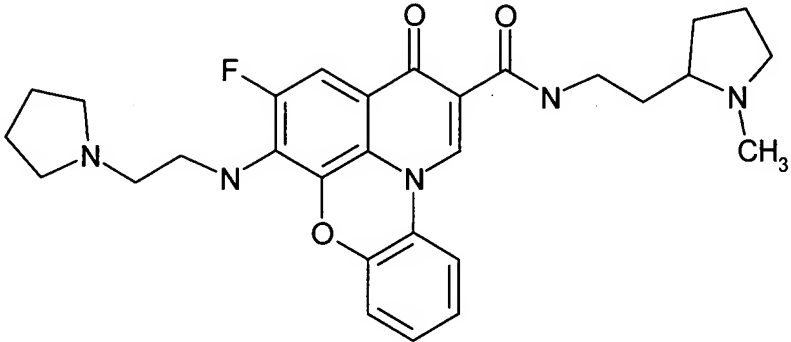
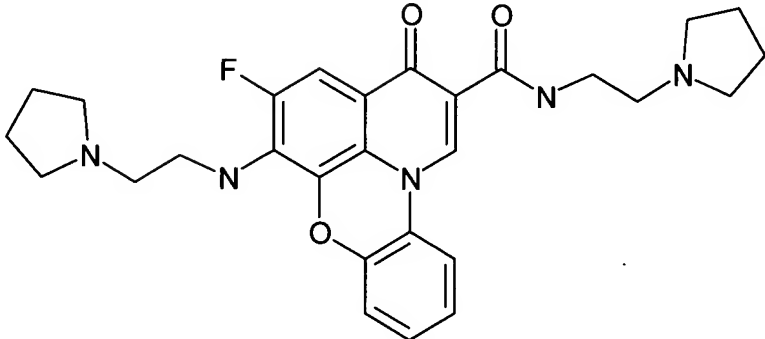
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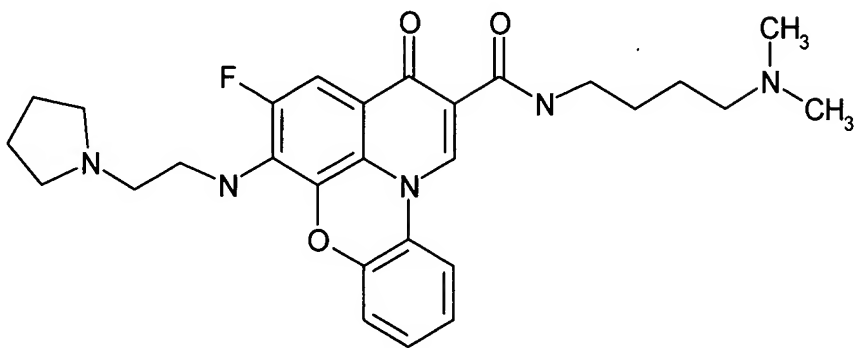
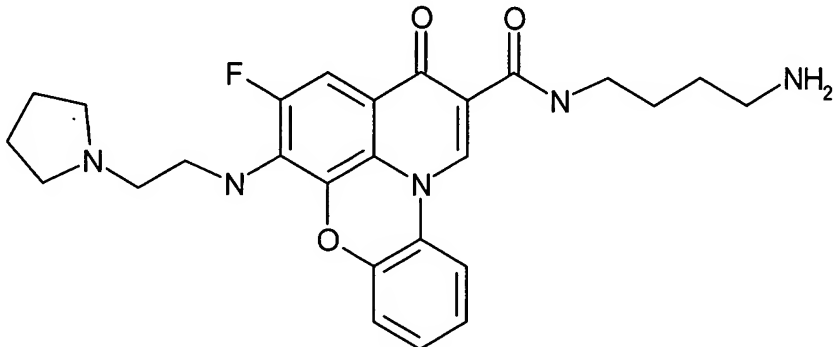
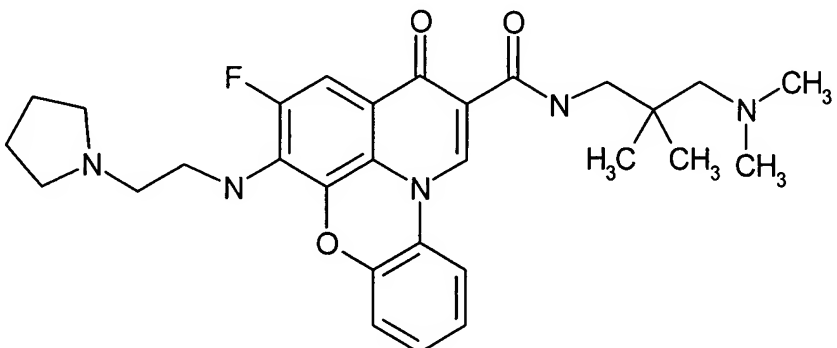


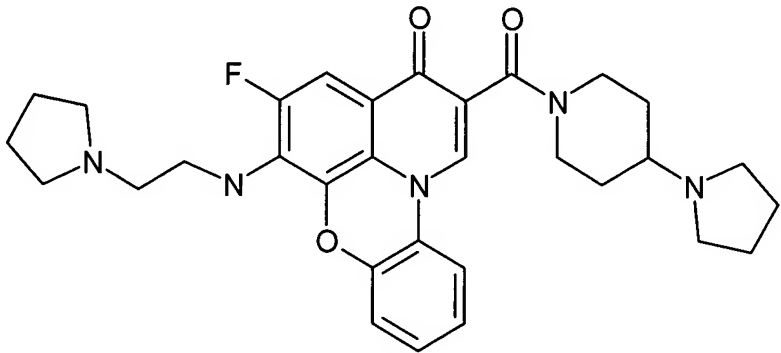
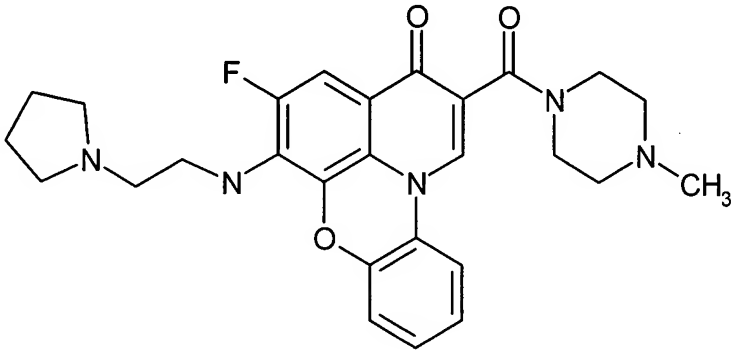
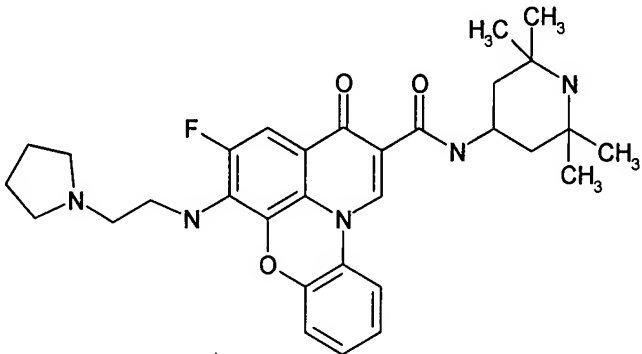
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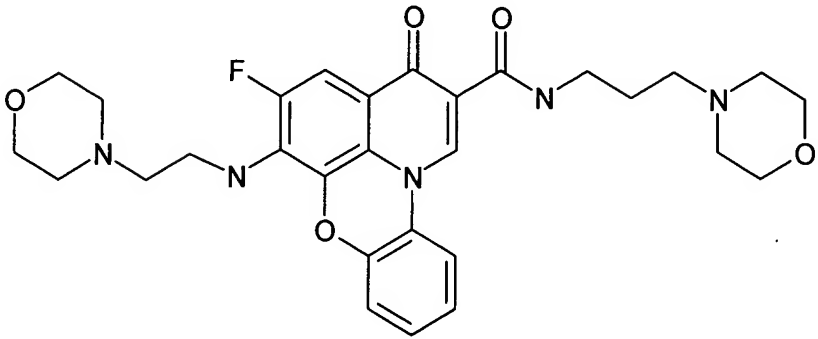
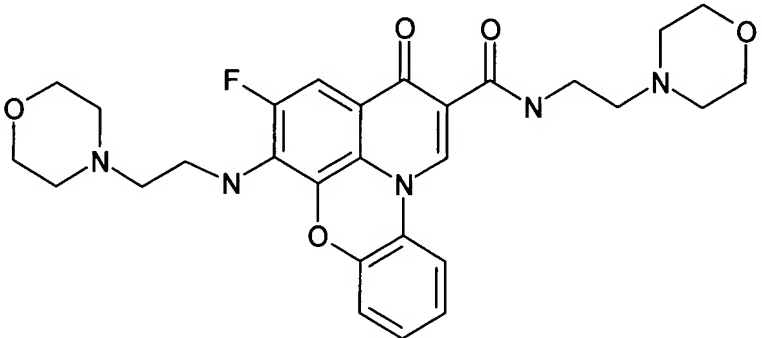
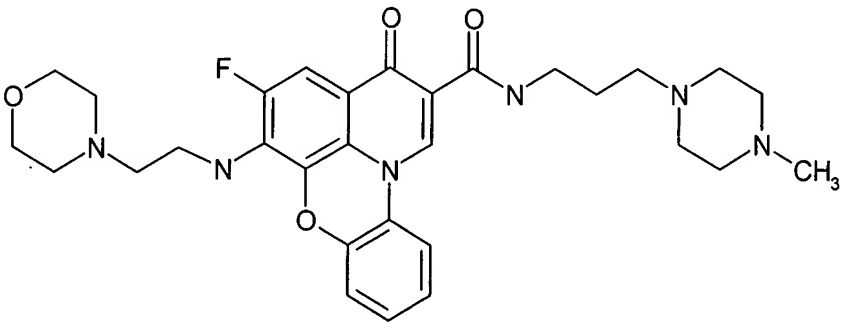
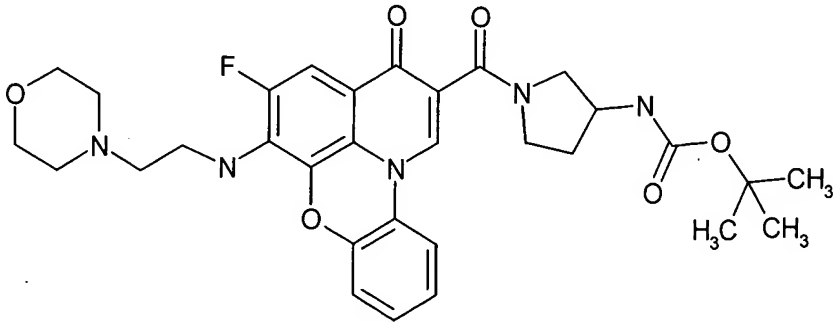
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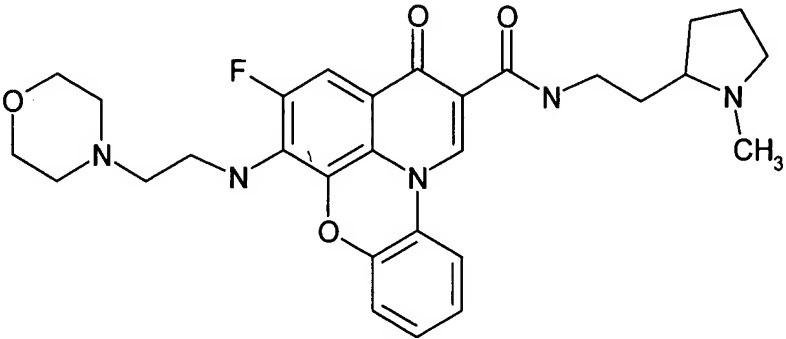
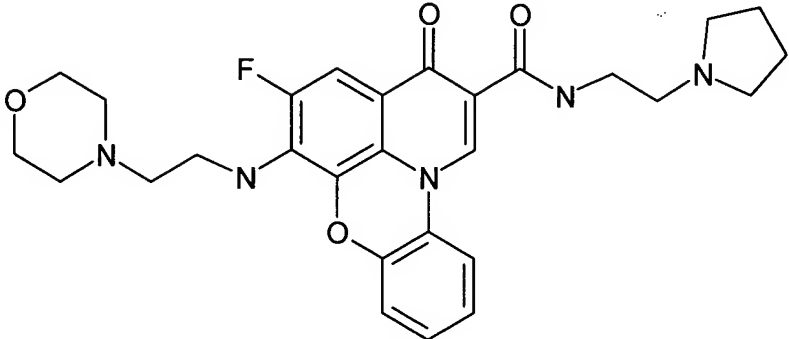
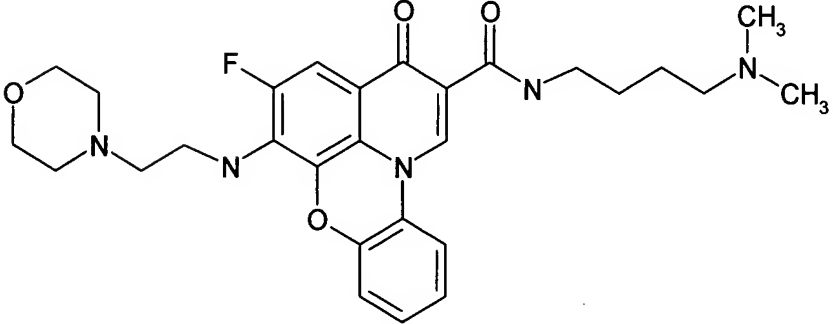
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1376			

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1379			

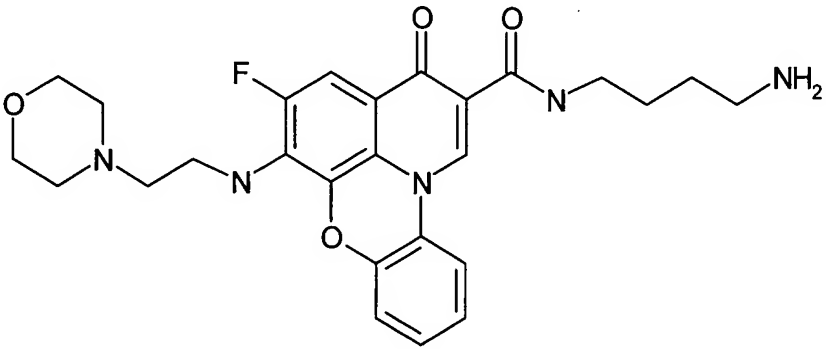
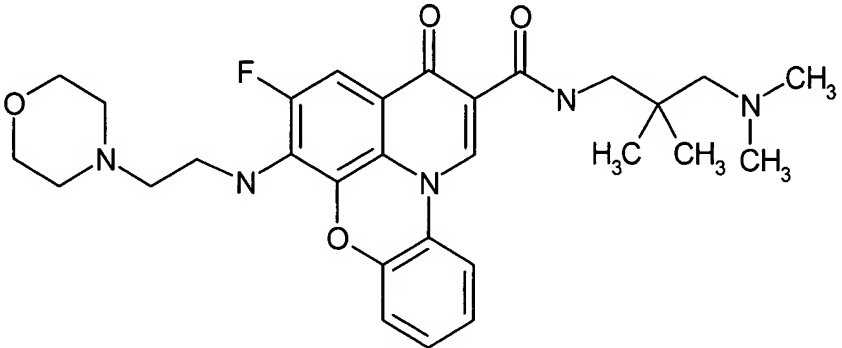
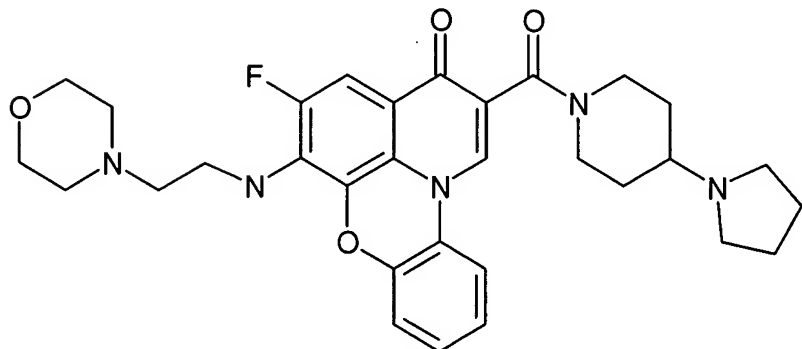
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1382			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1385			

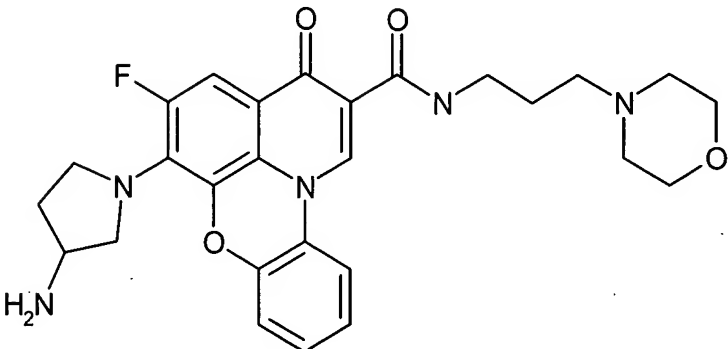
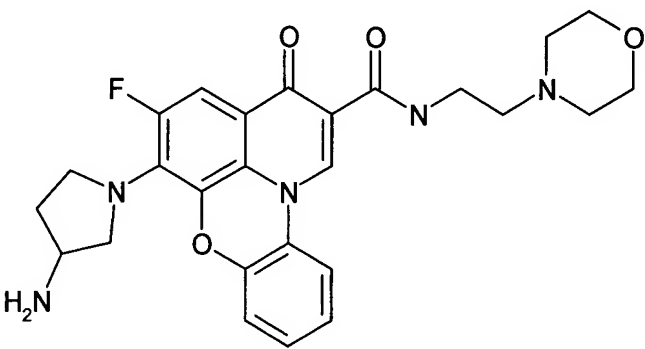
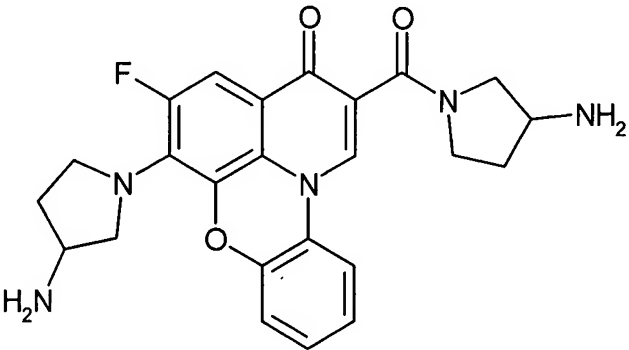
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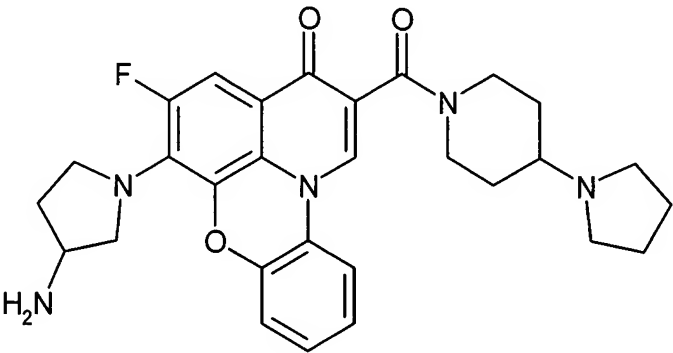
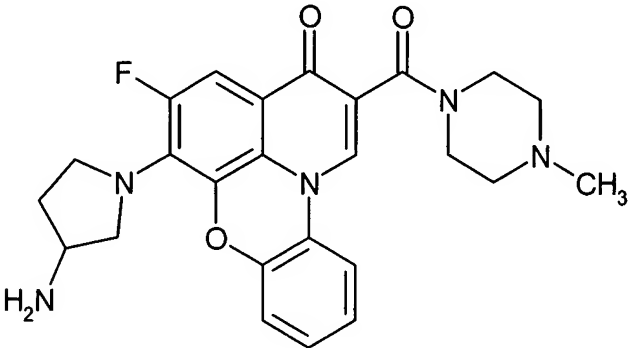
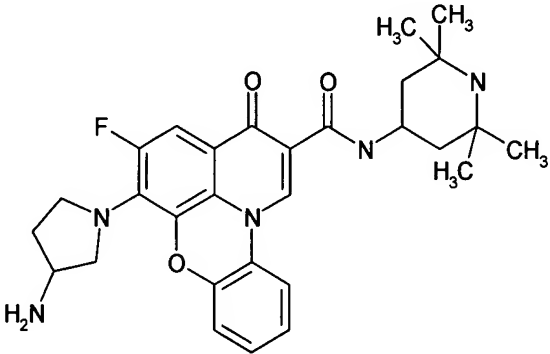


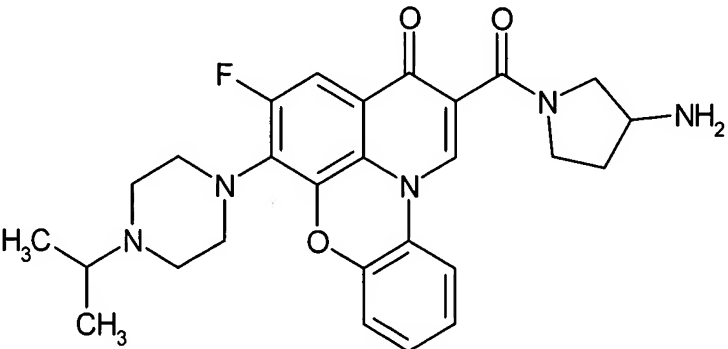
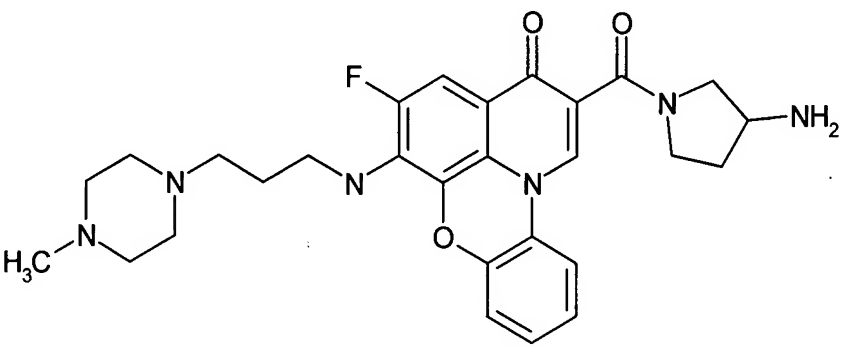
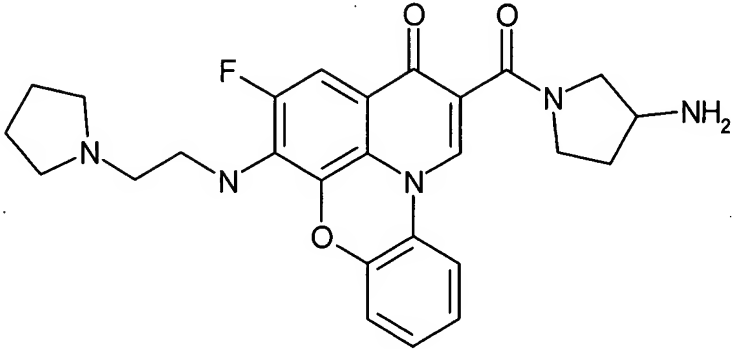
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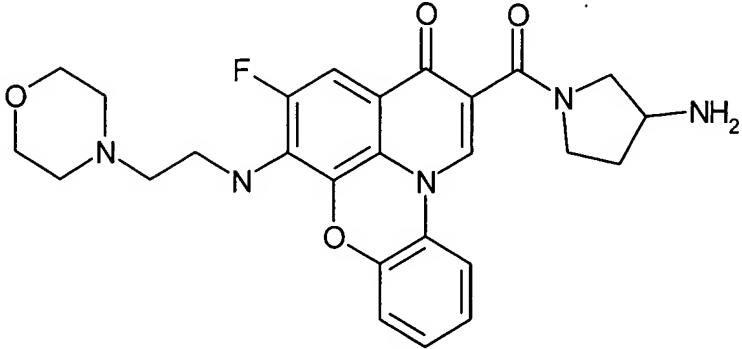
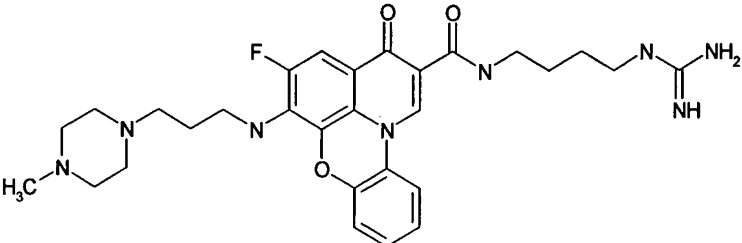
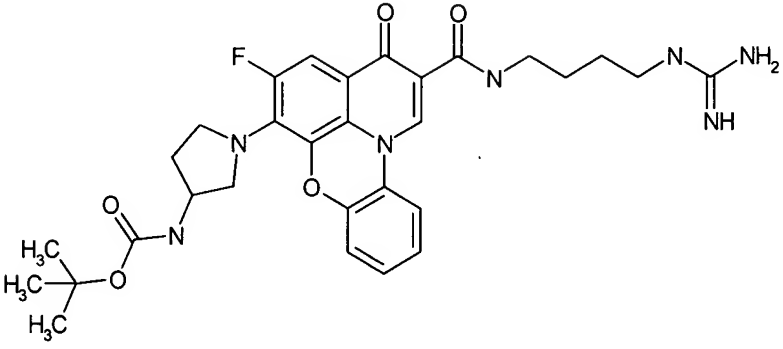
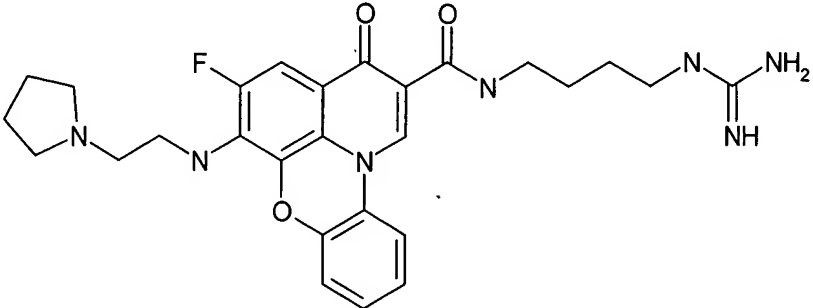
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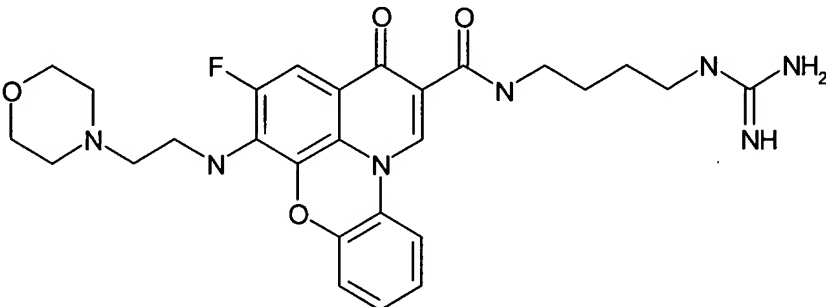
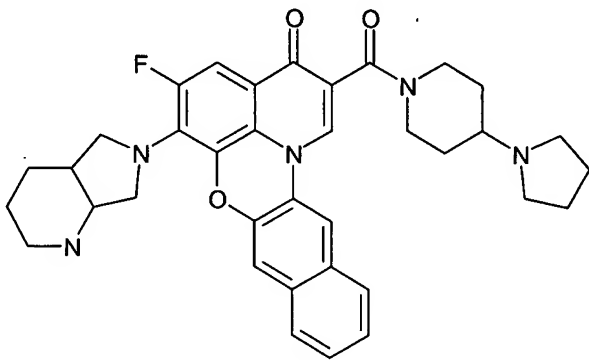
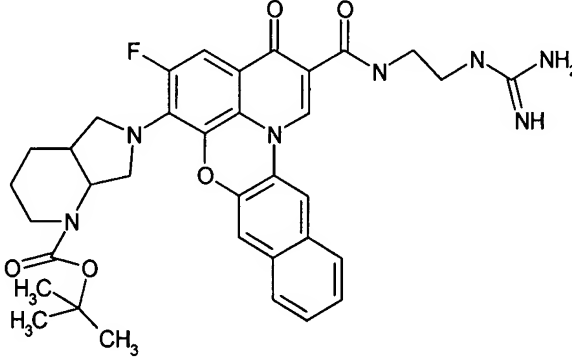
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1400			
1401			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1402			
1403			
1404			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1405			
1406			
1407			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1410			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1414			

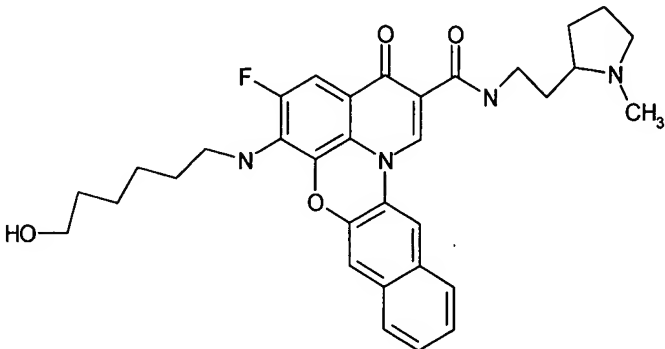
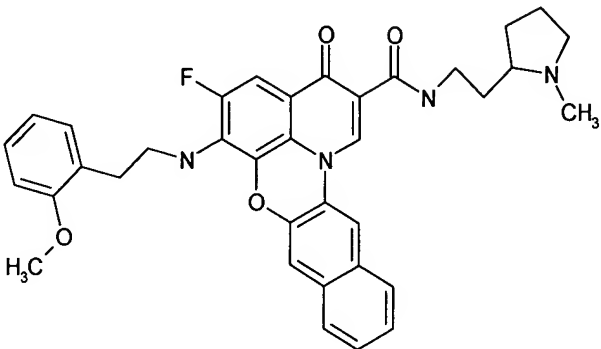
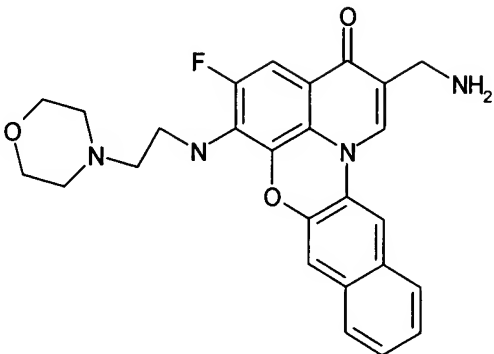
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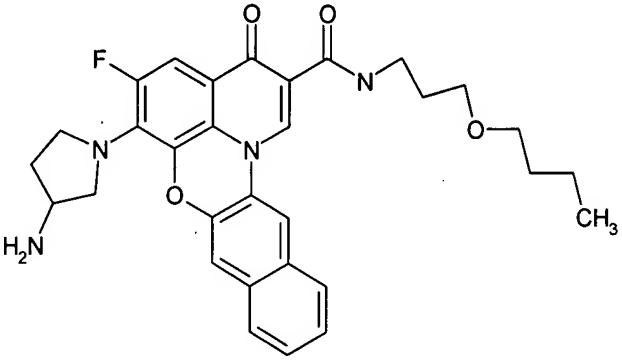
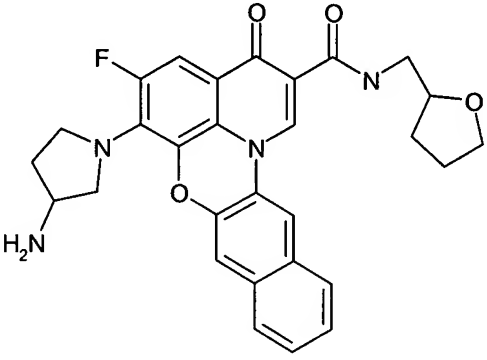
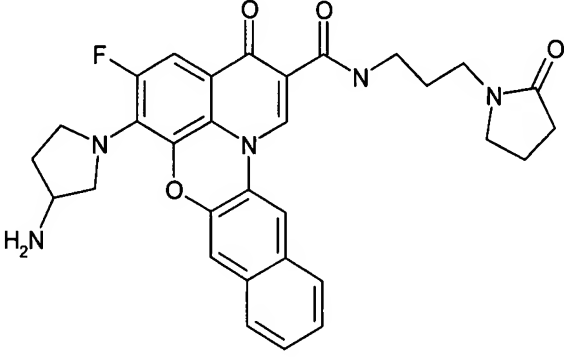


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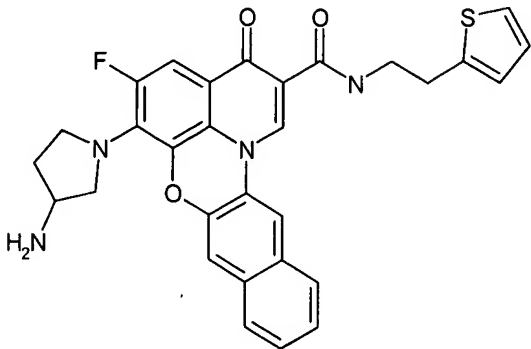
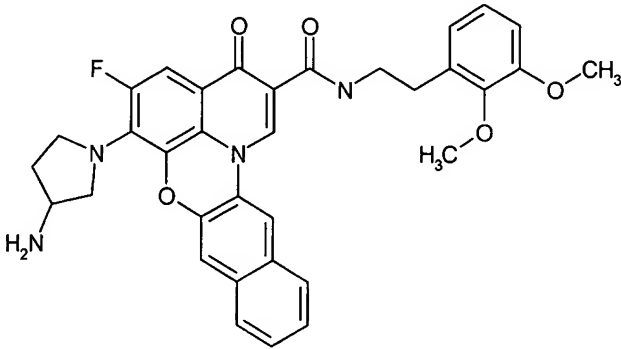
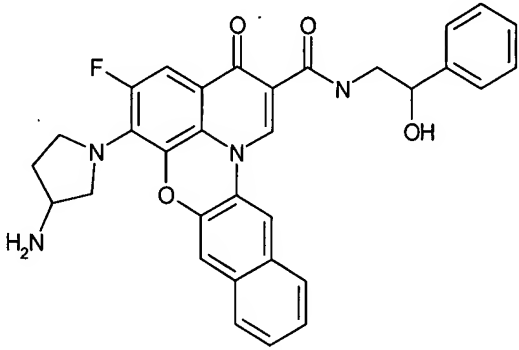
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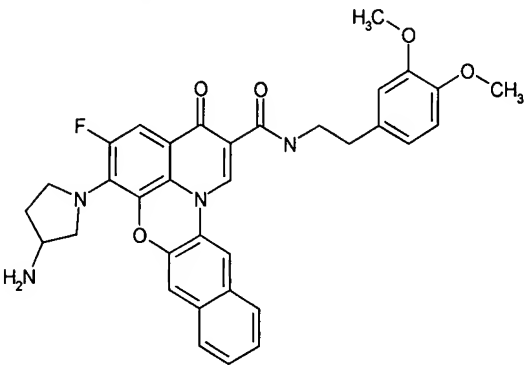
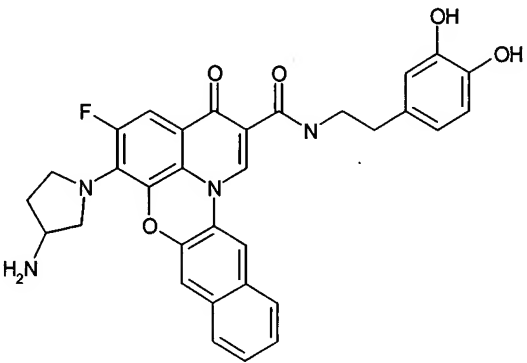
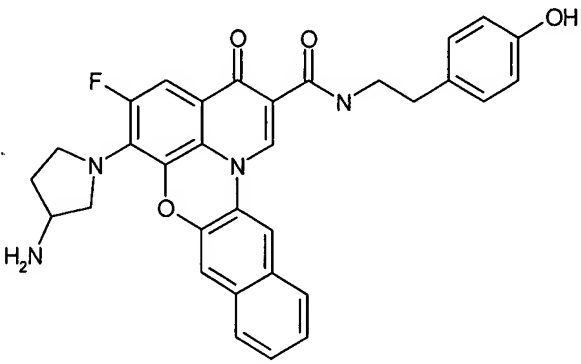
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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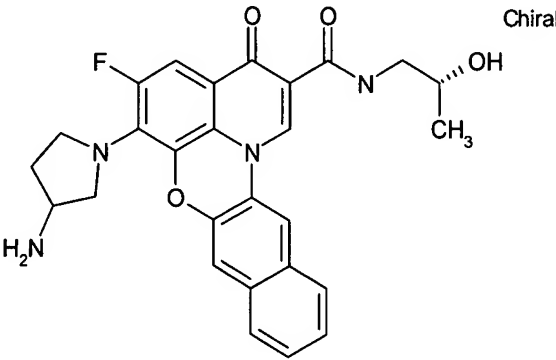
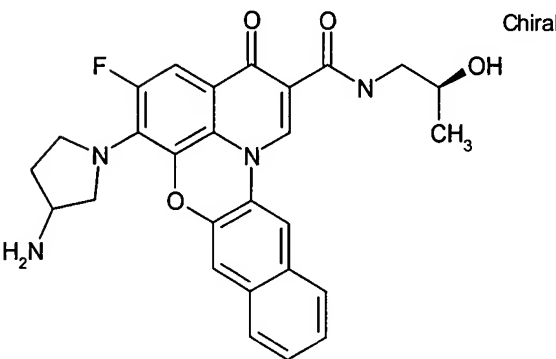
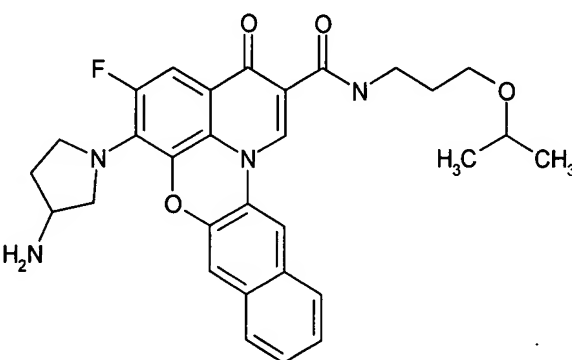
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	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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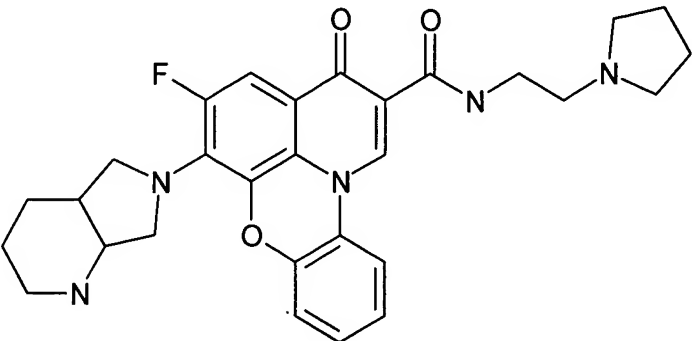
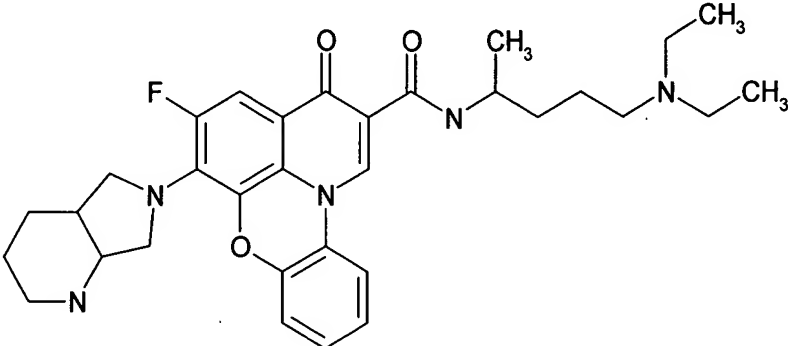
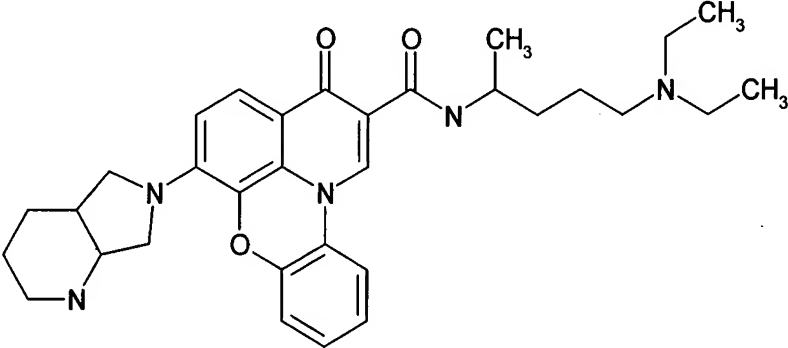
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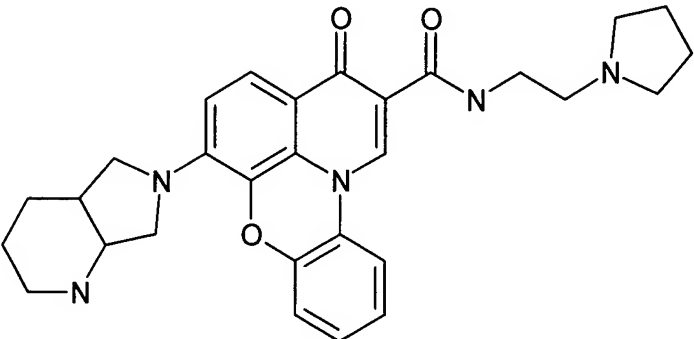
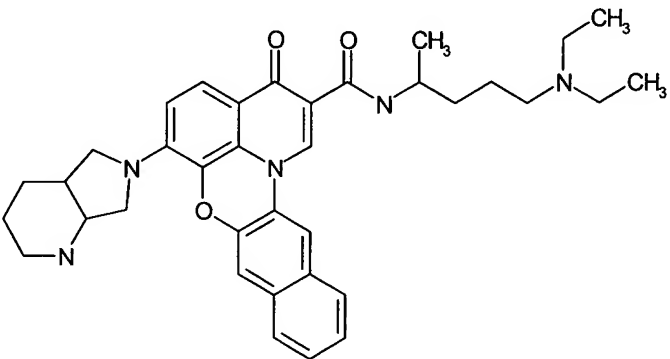
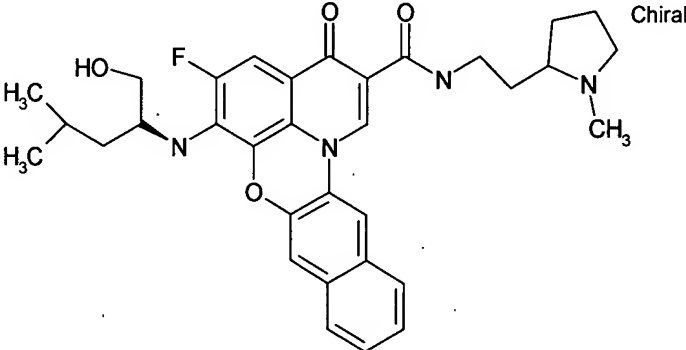
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1441			



	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1444			

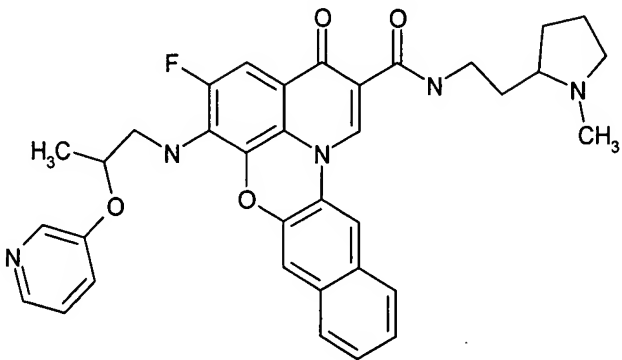
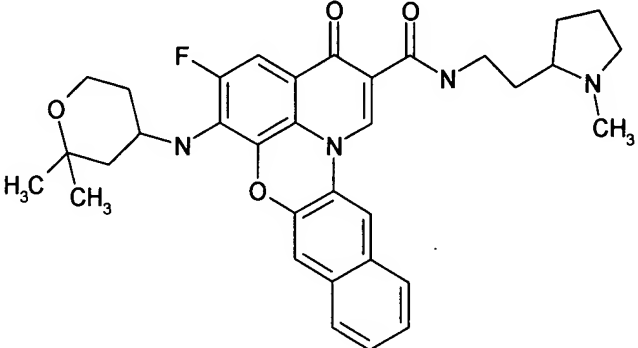
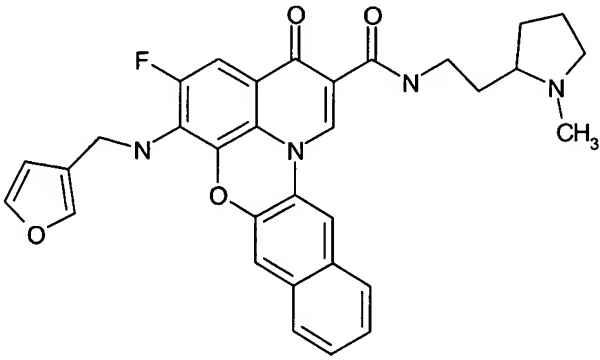
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1447			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1449			
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1452			
1453			

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1454			
1455			
1456			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
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1458			
1459			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1460			
1461			
1462			

	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1463			
1464			
1465			



	Structure	Stop Data c-Myc $\mu$ M	MTS Data Hella $\mu$ M
1466	